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(54) Title: INHIBITORS OF FATTY ACID AMIDE HYDROLASE

(57) Abstract: Improved competitive inhibitors of FAAH employ an α-keto heterocyclic pharmacophore and a binding subunit having a ?-unsaturation. The α-keto heterocyclic pharmacophore and a binding subunit are attached to one another, preferably by a hydrocarbon chain. The improvement lies in the use of a heterocyclic pharmacophore selected from oxazoles, oxadiazoles, thiazoles, and thiadiazoles that have alkyl or aryl substituents at their 4 and/or 5 positions. The improved competitive inhibitors of FAAH display enhanced activity over conventional competitive inhibitors of FAAH.

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INHIBITORS OF FATTY ACID AMIDE HYDROLASE

Description

Technical Field:

The present invention relates to inhibitors of fatty acid hydrolase. More particularly, the invention relates to inhibitors of fatty acid hydrolase of the type having a heterocyclic head group attached to a tail region.

Background:

Fatty acid amide hydrolase (FAAH) is an integral membrane protein that hydrolyzes a wide range of oleyl and arachidonyl amides, the CB1 agonist 2-arachidonylglycerol, the related 1-arachidonylglycerol and 1-oleylglycerol, and methyl arachidonate, illustrating a range of bioactive fatty acid amide or ester substrates. (W. Lang, et al., (1999) *J. Med. Chem.* **42**, 896–902; S.K. Goparaju, et al., (1998) *FEBS Lett.* **442**, 69–73; Y. Kurahashi, et al., (1997) *Biochem. Biophys. Res. Commun.* **237**, 512–515; and T. Bisogno, et al., (1997) *Biochem. J.* **322**, 671. Di Marzo, V., T. Bisogno, et al., (1998) *Biochem. J.* **331**, 15–19). The distribution of FAAH in the CNS suggests that it also degrades neuromodulating fatty acid amides at their sites of action and is intimately involved in their regulation (E.A. Thomas, et al., (1997) *J. Neurosci. Res.* **50**, 1047–1052). Although a range of fatty acid primary amides are hydrolyzed by the enzyme, FAAH appears to work most effectively on arachidonyl and oleyl substrates (B.F. Cravatt, et al., (1996) *Nature* **384**, 83–87; and D.K. Giang, et al., (1997) *Proc. Natl. Acad. Sci. USA* **94**, 2238–2242). FAAH was referred to as oleamide hydrolase and anandamide amidohydrolase in early studies.

A class of FAAH inhibitor represented by the formula **A**-**B**-**C** has been disclosed by Dale Boger (US Patent No. 6,462,054). In this formula, **A** is an α-keto heterocyclic pharmacophore for inhibiting the fatty acid amide hydrolase; **B**

is a chain for linking **A** and **C**, said chain having a linear skeleton of between 3 and 9 atoms selected from the group consisting of carbon, oxygen, sulfur, and nitrogen, the linear skeleton having a first end and a second end, the first end being covalently bonded to the α-keto group of **A**, with the following proviso: if the first end of said chain is an α-carbon with respect to the α-keto group of **A**, then the α-carbon is optionally mono- or bis-functionalized with substituents selected from the group consisting of fluoro, chloro, hydroxyl, alkoxy, trifluoromethyl, and alkyl; and **C** is a binding subunit for binding to FAAH and enhancing the inhibition activity of said α-keto heterocyclic pharmacophore, said binding subunit having at least one π-unsaturation situated within a π-bond containing radical selected from a group consisting of aryl, alkenyl, alkynyl, and ring structures having at least one unsaturation, with or without one or more heteroatoms, said bind subunit being covalently bonded to the second end of the linear skeleton of **B**, the π-unsaturation within the π-bond containing radical being separated from the α-keto group of **A** by a sequence of no less than 4 and no more than 9 atoms bonded sequentially to one another, inclusive of said linear skeleton.

What is needed are FAAH inhibitors having a head group attached to a tail region, the head group having one or more heterocycles for achieving enhanced activity with respect to the inhibition of fatty acid amide hydrolase.

Summary:

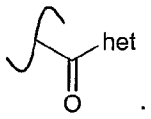
The invention is directed to improved competitive inhibitors of FAAH that employ an α-keto heterocyclic pharmacophore and a binding subunit having a π-unsaturation. The α-keto heterocyclic pharmacophore and a binding subunit are attached to one another, preferably by a hydrocarbon chain. The improvement lies in the use of a heterocyclic pharmacophore selected from oxazoles, oxadiazoles, thiazoles, and thiadiazoles that include alkyl or aryl substituents at their 4 and/or 5 positions. The improved competitive inhibitors of FAAH display enhanced activity over conventional competitive inhibitors of FAAH.

One aspect of the invention is directed to an inhibitor of fatty acid amide hydrolase represented by the following formula:

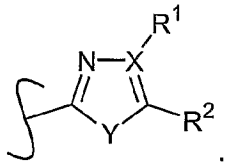
A-B-C.

In the above formula, A is an inhibition subunit, B is a linkage subunit, and C is a binding subunit.

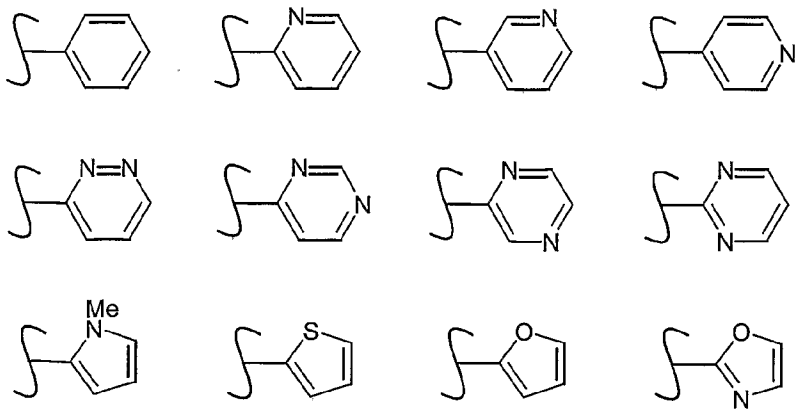
The inhibition subunit A is an α-keto heterocyclic pharmacophore for inhibiting the fatty acid amide hydrolase. The α-keto heterocyclic pharmacophore being represented by the following formula:

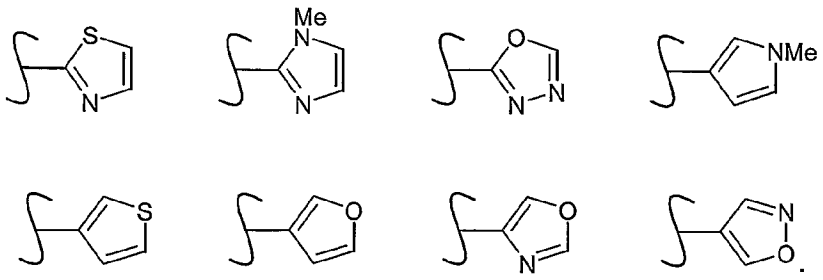


In the above formula, "het" is represented by the following structure:



In the above structure, X is selected from the group consisting of carbon and nitrogen; **Y** is selected from the group consisting of oxygen and sulfur; R^1 and R^2 are radicals independently selected from the group consisting of hydrogen, C1-C6 alkyl, aromatic ring, and heteroaromatic ring. In a preferred embodiment, R^1 and R^2 are radicals independently selected from the group consisting of hydrogen, C1-C6 alkyl, and radicals represented by the following structures:





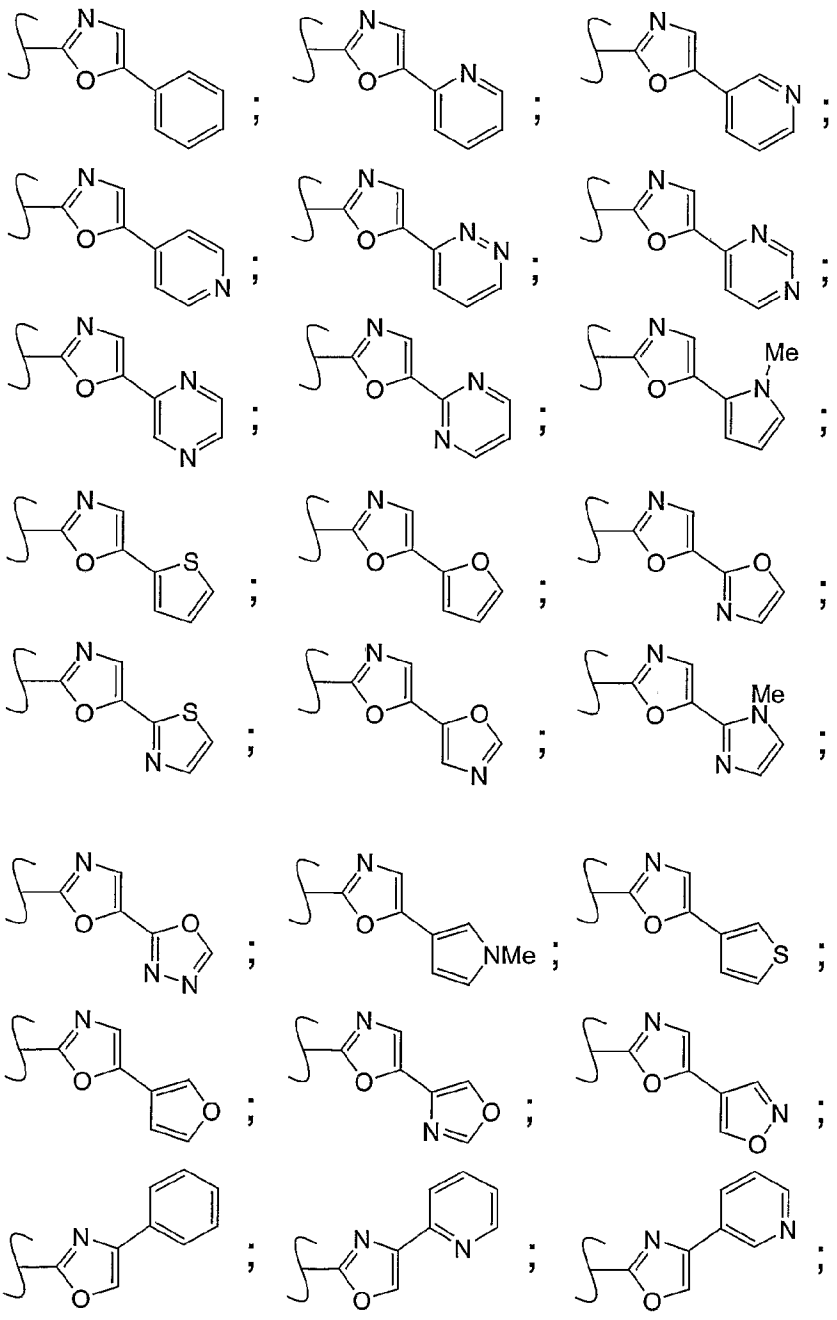
However, there is are two provisos, viz., 1.) R^1 and R^2 cannot both be hydrogen; and 2.) if X is nitrogen, R^1 is absent.

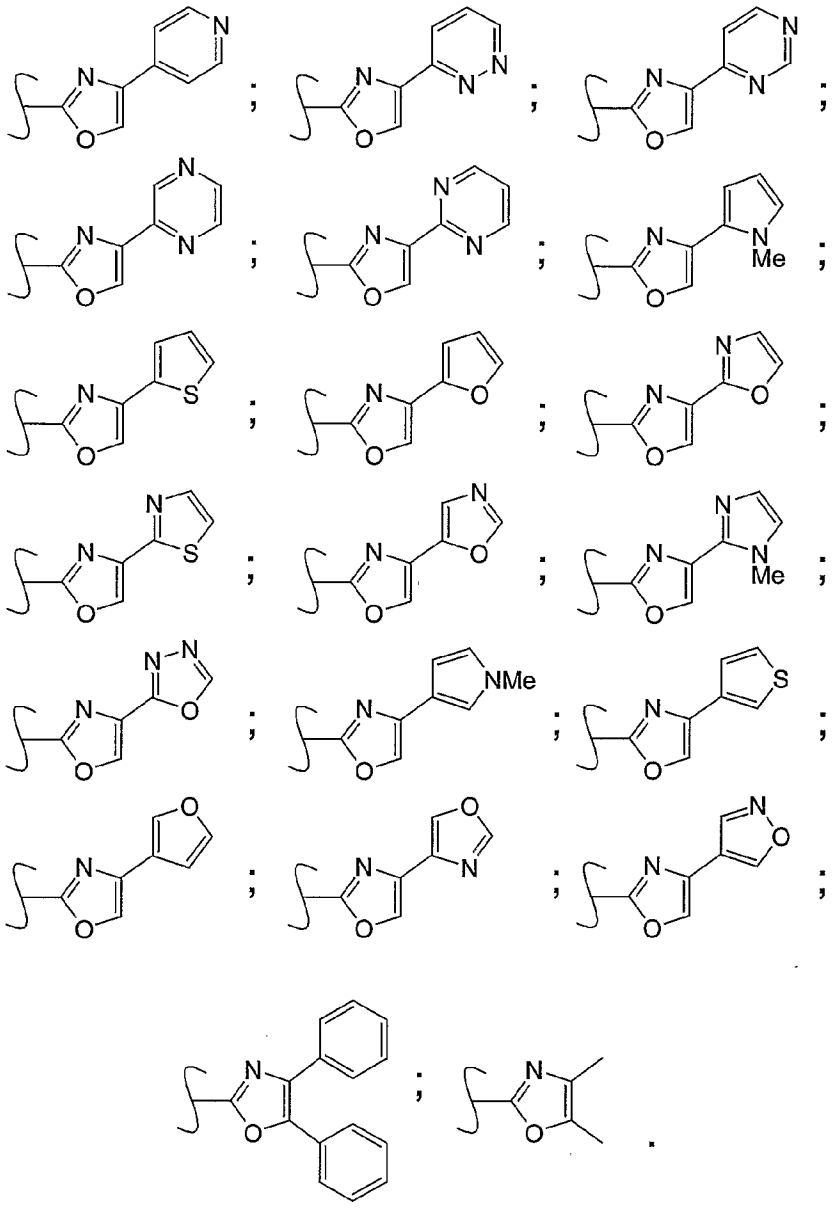
The linkage subunit **B** is a chain for linking the inhibition subunit **A** and the binding subunit **C** and for enabling the binding subunit **C** to bind to the binding region on the fatty acid amide hydrolase while the inhibition subunit A simultaneously inhibits the fatty acid amide hydrolase. The chain has a linear skeleton of between 3 and 9 atoms selected from the group consisting of carbon, oxygen, sulfur, and nitrogen, the linear skeleton having a first end and a second end, the first end being covalently bonded to the α-keto group of **A**. However, there is a proviso that, if the first end of said chain is an α-carbon with respect to the α-keto group of the inhibition subunit **A**, then the α-carbon is optionally mono- or bis-functionalized with substituents selected from the group consisting of fluoro, chloro, hydroxyl, alkoxy, trifluoromethyl, and alkyl.

The binding subunit **C** is a π-bond containing radical having a π-unsaturation. The binding subunit **C** is selected from a group consisting of aryl, alkenyl, alkynyl, and ring structures having at least one unsaturation, with or without one or more heteroatoms. The binding subunit **C** is covalently bonded to the second end of the linkage subunit **B**. The π-unsaturation within the π-bond containing radical is separated from the α-keto group of **A** by a sequence of no less than 3 and no more than 9 atoms bonded sequentially to one another, inclusive of the linear skeleton, for enabling the π-unsaturation to bind to the binding region of the fatty acid amide hydrolase while the inhibition subunit **A**

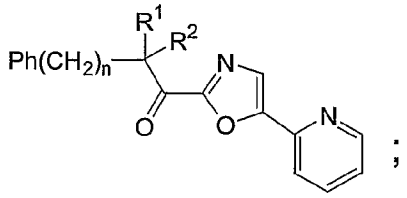
inhibits the fatty acid amide hydrolase. However, there is a proviso that **C** is optionally C1-C10 alkyl.

In a further preferred embodiment, "het" of the α-keto heterocyclic pharmacophore is selected from the following group:





In a further preferred embodiment, the inhibitor of fatty acid amide hydrolase is represented by the following structure:



In the above structure, R^1 and R^2 are independently selected from the group consisting of hydrogen, fluoro, chloro, hydroxyl, alkoxy, trifluoromethyl, and alkyl; and "n" is an integer between 2 and 8.

A further aspect of the invention is directed to processes for inhibiting fatty acid amide hydrolase. The process employs the step of contacting the fatty acid amide hydrolase with an inhibiting concentration of an inhibitor of the type described above. Upon contacting the fatty acid amide, the binding subunit **C** of the inhibitor binds to the binding region of the fatty acid amide hydrolase for enhancing the inhibition activity of the inhibitor.

Brief Description of Figures:

Figure 1 illustrates two tables that list the K_i's for the various compounds tested.

Figure 2 is a continuation of the second table of Figure 1 that lists the K_i's for the 4- and 5-heteroaryl substituted α-keto oxazole inhibitors of FAAH.

Figure 3 illustrates a table of the K_i's of α-keto oxazolopyridine inhibitors of FAAH.

Figure 4 illustrates a table showing the systematic variation in the side chain and its effects on the activity of the compounds listed. An exemplary head group is used in this series.

Figure 5 illustrates the aryl-substituted heterocycles **206** and **207** and their method of synthesis from either the 4- or 5-bromo compounds.

Figure 6 illustrates a table that shows the change in K_i's of the compounds by the presence or absence of a double bond in the C18 tail of α-keto heterocycle inhibitors of FAAH.

Figure 7 illustrates a table that shows the effect of modifying the fatty acid side chain of α-keto oxazolopyridine inhibitors of FAAH on the K_i's of the compounds.

Figure 8 illustrates a table that shows first generation inhibitors and their IC_{50}'s with FAAH.

Figure 9 illustrates a table that shows second generation inhibitors and their IC_{50}'s with FAAH.

Figure 10 illustrates a series of reactions that disclose how the substituted oxazole inhibitors are synthesized.

Figure 11 illustrates a bar graph showing the reduced thermal pain responses 60 minutes following the injection of OL-135 (10 mg/kg, i.p.).

Figure 12 illustrates a bar graph showing the reduced thermal pain responses 60 minutes following the injection of OL-135 (10 mg/kg, i.p.).

Figure 13 illustrates a bar graph that shows SR 141716A blocking the analgesic effects of OL-135 in the tail immersion test.

Figure 14 illustrates a bar graph that shows SR 141716A blocking the analgesic effects of OL-135 in the hot plate test.

Figure 15 illustrates how the ester is functionalized at the alpha position with fluorine, hydroxyl and trifluoromethyl groups.

Figure 16 illustrates the methods by which chlorine, alpha-alkyl-alpha-hydroxyl, alpha-alkyl-alpha-trifluoromethyl, and alpha-alkyl-alpha-fluoro groups may be added to an ester.

Detailed Description:

Improved competitive inhibitors of FAAH were developed employing an α-keto heterocyclic pharmacophore and a binding subunit having a π-unsaturation. The α-keto heterocyclic pharmacophore and a binding subunit are attached to one another, preferably by a hydrocarbon chain. The improvement lies in the use of a heterocyclic pharmacophore selected from oxazoles, oxadiazoles, thiazoles, and thiadiazoles that include alkyl or aryl substituents at their 4 and/or 5 positions. The improved competitive inhibitors of FAAH display enhanced activity over conventional competitive inhibitors of FAAH which employ non-azole heterocyclic pharmacophores and/or heterocyclic pharmacophores that lack aryl or alkyl substituents.

The improved competitive inhibitors of FAAH disclosed herein confirm that incorporation of an unsaturation into the fatty acid chain increases inhibitor potency. The incorporation of a benzene ring proved to be particularly effective. Similarly, the electrophilic carbonyl was confirmed to be required for potent enzyme inhibition with respect to the competitive inhibitors of FAAH disclosed herein.

Methods

Inhibition Studies:

All enzyme assays were performed at 20–23 °C using a solubilized liver plasma membrane extract containing FAAH in a reaction buffer of 125 mM Tris, 1 mM EDTA, 0.2% glycerol, 0.02% Triton X-100, 0.4 mM HEPES, pH 9.0 buffer (M.P. Patricelli, et al., (1998) *Bioorg. Med. Chem. Lett.* **8**, 613–618; and J.E. Patterson, et al., (1996) *J. Am. Chem. Soc.* **118**, 5938–5945). The initial rates of hydrolysis were monitored by following the breakdown of ^{14}C-oleamide to oleic acid as previously described (B.F. Cravatt, et al., (1995) *Science* **268**, 1506–1509; and M.P. Patricelli, et al., (1998) *Bioorg. Med. Chem. Lett.* **8**, 613–618). The inhibition was reversible, non time-dependent and linear least squares fits were used for all reaction progress curves and R^2 values were consistently >0.97. IC_{50} values were determined from the inhibition observed at

3–5 different inhibitor concentrations (from three or more trials at each inhibitor concentration) using the formula $IC_{50} = [I]/[(K_0/K_i)–1]$, where K_0 is the control reaction rate without inhibitor and K_i is the rate with inhibitor at concentration [I] (K. Conde- Frieboes, et al., (1996) *J. Am. Chem. Soc.* **118**, 5519–5525). K_i values were determined by the Dixon method (x-intercepts of weighted linear fits of [I] versus 1/rate plots at constant substrate concentration, which were converted to K_i values using the formula $K_i = –x_{int}/[1+[S]/K_m]$). Previous work demonstrated the rat and human enzyme are very homologous (84%), exhibit near identical substrate specificities, and incorporate an identical amidase consensus sequence and SH3 binding domain suggesting the observations made with rat FAAH will be similar if not identical to those of human FAAH (B.F. Cravatt, et al., (1996) *Nature* **384**, 83–87; and D.K. Giang, et al., (1997) *Proc. Natl. Acad. Sci. USA* **94**, 2238–2242).

Detailed Description of Figures:

Figure 1 illustrates two tables that list the K_i's for the various compounds tested. The first table shows that the oxazole and oxadiazole are over 1000 times more potent than the thiazole. Interestingly, the potency is very nearly recovered by the substitution of another nitrogen in the thiadiazole heterocycle. The second table shows the variations in the heterocycle in the 4- and 5-positions of the oxazole head group and its effect on K_i. Figure 2 is a continuation of the second table in Figure 1. One trend seen with the data is the increase in activity with nitrogen-containing heterocycles.

Figure 3 illustrates a table of the K_i's of α-keto oxazolopyridine inhibitors of FAAH. The clear trends are noted below the table. As seen in Figure 2 with the 4- and 5-aryl-substituted oxazole headgroup compounds, the introduction of a basic nitrogen in the ring leads to greatly enhanced activity. There is no large change in K_i with the change in nitrogen position.

Figure 4 illustrates a table showing the modifications in the fatty acid side chain and the effects on K_i. The trend is slightly different here than that of the

oxazolopyridine inhibitor tested earlier. A saturated dodecanoyl group on this 5-(2-pyridyl)-substituted oxazole gave a lower K_i than the favored alkylphenyl side chain. The difference between compounds **185** and **200** is only a factor of two.

Figure 5 illustrates compounds **206** and **207** and how a palladium-catalyzed cross-coupling reaction is used to synthesize them. The Suzuki coupling is accomplished by using catalytic palladium(0) dibenzylidene acetone in the presence of base and the desired aryl or heteroaryl boronic acid (Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2857-2483).

Figure 6 illustrates a table that shows the change in K_i's of the compounds by the presence or absence of a double bond in the C18 tail of α-keto heterocycle inhibitors of FAAH. The first three compounds show that the unsaturation in the chain is important for binding to such an extent that the binding constant is five-fold greater for the fully saturated chain. Essentially the same result is observed for the next two head groups.

Figure 7 illustrates a table that shows the effect of modifying the fatty acid side chain of α-keto oxazolopyridine inhibitors of FAAH on the K_i's of the compounds. This table compares the various hydrocarbon tail groups with each other and the general trends are summarized in the lines on the bottom of the chart. The best saturated chains are those with between 8 and 12 carbons. The phenyl-containing side chains are about 3 times as potent as the saturated side chains with this head group. The best K_i was 200 pM for this series of compounds.

Figure 8 illustrates a table that shows first generation inhibitors and their IC_{50}'s with FAAH. The value for the IC_{50} is approximately 10 times larger than the corresponding K_i's for this enzyme. A trifluoromethyl ketone is included for comparison with the designed inhibitors. The IC_{50}'s correspond well to the K_i's of the compounds. Again, compound **118** has both the lowest IC_{50} and K_i.

Figure 9 illustrates a table that shows second generation inhibitors and their IC_{50}'s with FAAH. The second generation inhibitors show more variation in their IC_{50}'s compared to their corresponding K_i's.

Figure 10 illustrates a series of reactions that illustrate how the substituted oxazole inhibitors are synthesized. The first reaction at the top of the page shows how the 2-position on the oxazole is acylated. The oxazole is first lithiated with *n*-butyllithium, transmetallated with zinc chloride, the cuprate is formed by the addition of copper(I) iodide and then the cuprate is acylated with the acid chloride. The detailed procedure is described for compound **162** in the experimental section. The second method for the formation of the 2-acyl oxazoles is a standard lithiation and then acylation with the Weinreb amide. Compound **144** was synthesized by this method as outlined in the experimental section. The remaining two reactions show the retrosynthesis for the 4- or 5-substituted heterocycle. In the last reaction, X is a halogen or some other leaving group.

Figure 11 illustrates a bar graph showing the reduced thermal pain responses 60 minutes following the injection of OL-135 (10 mg/kg, i.p.). This test is the tail withdrawal test and there is no effect with the vehicle while there is marked delay after administration of the OL-135. [$p < 0.001$; N=12 mice per group; results shown as means ± S.E.]

Figure 12 illustrates a bar graph showing the reduced thermal pain responses 60 minutes following the injection of OL-135 (10 mg/kg, i.p.). This test is the hot plate test and there is no effect with the vehicle and there is some delay after administration of the OL-135. [$p < 0.01$; N=12 mice per group; results shown as means ± S.E.]

Figure 13 illustrates a bar graph that shows SR 141716A blocking the analgesic effects of OL-135 in the tail immersion test. The mice received an i.p. injection of vehicle or SR 141716A (3 mg/kg); 10 minutes later all subjects were given OL-135 (10 mg/kg, i.p.) and then evaluated in the tail immersion test one

hour after the second injection. ($p < 0.001$ for OL-135-treated mice that were pretreated with vehicle versus either their pre-injection baseline latencies or OL-135 treated mice that were pretreated with SR 141716A.) Results are shown as means ± S. E. N=6 mice/group.

Figure 14 illustrates a bar graph that shows SR 141716A blocking the analgesic effects of OL-135 in the hot plate test. The mice received an i.p. injection of vehicle or SR 141716A (3 mg/kg); 10 minutes later all subjects were given OL-135 (10 mg/kg, i.p.) and then evaluated in the hot plate test one hour after the second injection. [$p < 0.001$ for OL-135-treated mice that were pretreated with vehicle versus either their pre-injection baseline latencies or OL-135 treated mice that were pretreated with SR 141716A. Results are shown as means ± S. E. N=6 mice/group.]

Figure 15 illustrates how the ester is functionalized at the alpha position with fluorine, hydroxyl and trifluoromethyl groups. An asymmetric method for making a chiral alpha-fluoro ester is given, but one familiar with the art will know how to accomplish making the trifluoromethyl derivative in an asymmetric fashion. These methods assume that any functional groups present in "R" have suitable protection.

Figure 16 illustrates the methods by which chlorine, alpha-alkyl-alpha-hydroxyl, alpha-alkyl-alpha-trifluoromethyl, and alpha-alkyl-alpha-fluoro groups may be added to an ester. Depending on what "R" is, some of these esters or the corresponding acids may be commercially available. A Mitsunobu reaction is done to obtain the alpha-chloro compound from the corresponding alpha-hydroxy ester. An asymmetric hydroxylation of an enolate of an alpha-alkyl ester is accomplished by using an asymmetric oxaziridine (I). The last two products in this figure are obtained as racemates.

Experimental

1-([1,3,4]Oxadiazol-2-yl)octadec-9-en-1-one. (140) A suspension of the Dess-Martin periodinane (1.2 equiv, 0.025 mmol, 11 mg) in anhydrous CH_2Cl_2 (0.5 mL) was treated with a solution of 1-([1,3,4]oxadiazol-2-yl)octadec-9-en-1-ol (7 mg, 0.021 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at rt under N_2. After 6 h the suspension was diluted with Et_2O (10 mL), and poured into a solution of $Na_2S_2O_3$ (77 mg) in saturated aqueous $NaHCO_3$ (6.5 mL). The mixture was stirred at rt for 1 h and the layers were separated. The ethereal layer was washed with saturated aqueous $NaHCO_3$ (1 x 10 mL) and H_2O (1 x 10 mL), dried ($MgSO_4$), filtered and evaporated. Flash chromatography (SiO_2, 1.5 cm x 15 cm, 2% MeOH-CH_2Cl_2) afforded 1-([1,3,4]oxadiazol-2-yl)octadec-9-en-1-one (**140**) (5 mg, 0.016 mmol, 75% yield) as a dark yellow oil: ^1H NMR ($CDCl_3$, 250 MHz) d 9.34 (s, 1H), 5.42-5.26 (m, 2H), 3.04 (t, J = 7.4 Hz, 2H), 2.12-1.87 (m, 4H), 1.82-1.75 (m, 2H), 1.43-1.19 (m, 20H), 0.88 (br t, J = 6.8 Hz, 3H); IR ($CDCl_3$) u_{max} 2940, 2860, 1705, 1612, 1547, 1510, 1423, 1380 cm^{-1}; MALDI-FTMS (DHB) *m/z* 335.2689 ($C_{20}H_{34}N_2O_2 + H^+$ requires 335.2698).

1-([1,3,4]Thiadiazol-2-yl)octadec-9-en-1-one. (141) A suspension of the Dess-Martin periodinane (1.2 equiv, 0.013 mmol, 14 mg) in anhydrous CH_2Cl_2 (0.5 mL) was treated with a solution of 1-([1,3,4]thiadiazol-2-yl)octadec-9-en-1-ol (4 mg, 0.011 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at rt under N_2. After 10 h the suspension was diluted with Et_2O (10 mL), and poured into a solution of $Na_2S_2O_3$ (40 mg) in saturated aqueous $NaHCO_3$ (3.4 mL). The mixture was stirred at rt for 1 h and the layers were separated. The ethereal layer was washed with saturated aqueous $NaHCO_3$ (1 x 10 mL) and H_2O (1 x 10 mL), dried ($MgSO_4$), filtered and evaporated. Flash chromatography (SiO_2, 1.5 cm x 15 cm, 2% MeOH-CH_2Cl_2) afforded 1-([1,3,4]thiadiazol-2-yl)octadec-9-en-1-one (**141**) (3 mg, 0.008 mmol, 70% yield) as a dark yellow oil: MALDI-FTMS (DHB) *m/z* 351.2464 ($C_{20}H_{34}N_2OS + H^+$ requires 351.2470).

1-(5-Phenyloxazol-2-yl)-1-oxo-9(*Z*)-octadecene. (142) This material was prepared from 5-phenyloxazole (Van Leusen, A. M.; et al *Tetrahedron Lett.* **1972**, 2369-2372) using the procedure described for **162**. Column chromatography (SiO_2, 2.5 x 12 cm, 3% Et_2O-hexanes) afforded **142** (192 mg, 0.471 mmol, 72%) as a colorless crystalline powder: mp 32.0°C; MALDI-FTMS (NBA-NaI) *m/z* 432.2892 ($C_{27}H_{39}NO_2$ +Na^+ requires 432.2873).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-9(*Z*)-octadecene. (143) This material was prepared from 5-(2-pyridyl)oxazole (Saikachi, H.; et al. *Chem. Pharm. Bull.* **1979**, *27*, 793-796) using the procedure described for **162**. Column chromatography (SiO_2, 2.5 x 12 cm, 1% MeOH-$CHCl_3$) afforded **143** (64.3 mg, 0.157 mmol, 24%) as a pale yellow oil: MALDI-FTMS (NBA-NaI) *m/z* 433.2826 ($C_{26}H_{38}N_2O_2$ + Na^+ requires 433.2825).

1-Oxo-1-[5-(3-pyridyl)oxazol-2-yl]-9(*Z*)-octadecene. (144) A solution of BuLi in hexanes (2.5 M, 0.13 mL, 0.325 mmol, 1.05 equiv) was added dropwise to a solution of 5-(3-pyridyl)oxazole (Saikachi, H.; et al. *Chem. Pharm. Bull.* **1979**, *27*, 793-796) (45 mg, 0.308 mmol, 1.0 equiv) in anhydrous THF (5.0 mL) at -78°C, and the resulting solution was stirred at -78°C for 10 min. A solution of *N*-methoxy-*N*-methyloleoyl amide (100 mg, 0.308 mmol, 1.0 equiv) in anhydrous THF (2.0 mL) was added dropwise to the mixture, and the mixture was warmed to room temperature. After stirring for 16 h, water (15 mL) was added to the mixture, and the mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. Chromatography (SiO_2, 1.5 x 12 cm, $CHCl_3$) afforded **144** (40.4 mg, 0.098 mmol, 32% yield) as a colorless crystalline powder: mp 35.5-36.0°C; MALDI-FTMS (NBA-NaI) *m/z* 411.3002 ($C_{26}H_{38}N_2O_2$ + H^+ requires 411.3006).

1-Oxo-1-[5-(4-pyridyl)oxazol-2-yl]-9(*Z*)-octadecene. (145) This material was prepared from 5-(4-pyridyl)oxazole (Saikachi, H.; et al. *Chem. Pharm. Bull.* **1979**, *27*, 793-796) using the procedure described for **144**. Column chromatography

(SiO_2, 1.5 x 12 cm, 3% Et_2O-hexanes) afforded **145** (80.8 mg, 0.197 mmol, 64%) as a colorless solid: mp 48.0-49.0°C; MALDI-FTMS (NBA-NaI) *m/z* 411.3004 ($C_{26}H_{38}N_2O_2$ + H^+ requires 411.3006).

1-[5-(1-Methylpyrrol-2-yl)oxazol-2-yl]-1-oxo-9(*Z*)-octadecene. (150) This material was prepared from 5-(1-methylpyrrol-2-yl)oxazole (Saikachi, H.; et al. *Chem. Pharm. Bull.* **1979**, *27*, 793-796) using the procedure described for **162**. Column chromatography (SiO_2, 2.5 x 12 cm, 10% EtOAc-hexanes) afforded **150** (157 mg, 0.380 mmol, 59%) as a pale red oil: MALDI-FTMS (NBA-NaI) *m/z* 413.3172 ($C_{26}H_{40}N_2O_2$ + H^+ requires 413.3163).

1-Oxo-1-[5-(2-thienyl)oxazol-2-yl]-9(*Z*)-octadecene. (151) This material was prepared from 5-(2-thienyl)oxazole (Saikachi, H.; et al. *Chem. Pharm. Bull.* **1979**, *27*, 793-796) using the procedure described for **162**. Column chromatography (SiO_2, 2.5 x 12 cm, 5% Et_2O-hexanes) afforded **151** (165 mg, 0.397 mmol, 61%) as a pale yellow oil: MALDI-FTMS (NBA-NaI) *m/z* 416.2617 ($C_{25}N_{37}NO_2S$ + H^+ requires 416.2618).

1-[5-(2-Furyl)oxazol-2-yl]-1-oxo-9(*Z*)-octadecene. (152) This material was prepared from 5-(2-furyl)oxazole (Saikachi, H.; et al. *Chem. Pharm. Bull.* **1979**, *27*, 793-796) using the procedure described for **162**. Column chromatography (SiO_2, 2.5 x 12 cm, 3% Et_2O-hexanes) afforded **152** (177 mg, 0.443 mmol, 68%) as a pale orange oil: MALDI-FTMS (NBA-NaI) *m/z* 400.2849 ($C_{25}H_{37}NO_3$ + H^+ requires 400.2846).

1-Oxo-1-[5-(thiazol-2-yl)oxazol-2-yl]-9(*Z*)-octadecene. (154)

5-(Thiazol-2-yl)oxazole. Potassium carbonate (690 mg, 5.00 mmol, 1.0 equiv) was added to a solution of 2-thiazolecarboxaldehyde (566 mg, 5.00 mmol, 1.0 equiv) and (*p*-toluenesulfonyl)methyl isocyanide (TosMIC) (975 mg, 5.00 mmol, 1.0 equiv) in distilled methanol (15 mL) and the mixture was stirred at reflux for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was diluted with chloroform (70 mL) and washed

with water (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. Chromatography (SiO_2, 15 g, hexanes:ether = 5:1) afforded 5-(thiazol-2-yl)oxazole (626 mg, 4.11 mmol, 82%) as a pale yellow crystalline powder: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.96 (s, 1H), 7.90 (d, 1H, *J* = 3.3 Hz), 7.67 (s, 1H), 7.42 (d, 1H, *J* = 3.3 Hz).

1-Oxo-1-[5-(thiazol-2-yl)oxazol-2-yl]-9(*Z*)-octadecene. This material was prepared from 5-(thiazol-2-yl)oxazole using the procedure described for **162**. Column chromatography (SiO_2, 2.5 x 12 cm, 10% Et_2O-hexanes) afforded **154** (97.2 mg, 0.233 mmol, 36%) a pale yellow crystalline powder: mp 32.0-32.5°C; MALDI-FTMS (NBA-NaI) *m/z* 417.2572 ($C_{24}H_{36}N_2O_2S + H^+$ requires 417.2570).

1-Oxo-1-[5-(1-methylimidazol-2-yl)oxazol-2-yl]-9(*Z*)-octadecene. (155)

5-(1-Methylimidazol-2-yl)oxazole. This material was prepared in 79% yield from 1-methylimidazol-2-carboxaldehyde using the procedure described for 5-(thiazol-2-yl)oxazole. Column chromatography (SiO_2, 2.5 x 12 cm, 1% MeOH-$CHCl_3$) afforded 5-(1-methylimidazol-2-yl)oxazole (586 mg, 3.93 mmol, 79%) a yellow crystalline powder: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.96 (s, 1H), 7.48 (s, 1H), 7.14 (d, 1H, *J* = 1.1 Hz), 6.97 (d, 1H, *J* = 1.1 Hz), 3.86 (s, 3H).

1-Oxo-1-[5-(1-methylimidazol-2-yl)oxazol-2-yl]-9(*Z*)-octadecene. (155) This material was prepared from 5-(1-methylimidazol-2-yl)oxazole using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 50% Et_2O-hexanes) afforded **155** (44.6 mg, 0.108 mmol, 17%) a pale orange crystalline powder: mp. 46.0-47.0°C; MALDI-FTMS (NBA-NaI) *m/z* 414.3123 ($C_{25}H_{39}N_3O_2 + H^+$ requires 414.3115).

1-[5-(3-Thienyl)oxazol-2-yl]-1-oxo-9(*Z*)-octadecene. (158)

5-(3-Thienyl)oxazole. This material was prepared from thiophene-3-carboxaldehyde using the procedure described for 5-(thiazol-2-yl)oxazole (*vide supra*). Column chromatography (SiO_2, 2.5 x 12 cm, 10% EtOAc-hexanes) afforded 5-(3-thienyl)oxazole (519 mg, 3.43 mmol, 34%) a yellow oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.97 (s, 1H), 7.66 (dd, 1H, *J* = 2.9 and 1.1 Hz), 7.50 (dd, 1H, *J* = 4.9 and 2.9 Hz), 7.32 (s, 1H), 7.10 (d, 1H, *J* = 4.9 and 1.1 Hz).

1-Oxo-1-[5-(3-thienyl)oxazol-2-yl]-9(*Z*)-octadecene. (158) This material was prepared from 5-(3-thienyl)oxazole using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 5% EtOAc-hexanes) afforded **158** (102 mg, 0.244 mmol, 38%) a pale yellow oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.77 (dd, 1H, *J* = 2.6 and 1.5 Hz), 7.43 (dd, 1H, *J* = 5.0 and 2.6 Hz), 7.39 (dd, 1H, *J* = 5.0 and 1.5 Hz), 7.35 (s, 1H), 5.44-5.27 (m, 2H), 3.07 (t, 3H, *J* = 7.5 Hz), 2.10-1.93 (m, 4H), 1.84-1.69 (m, 2H), 1.47-1.19 (m, 20H), 0.87 (t, 3H, *J* = 6.6 Hz); IR (film) υ_{max} 3109, 3005, 2920, 2852, 1694, 1601, 1520, 1479, 1403, 1377, 1318, 1120, 1041, 976, 909, 857, 786, 733, 693, 610 cm^{-1}; MALDI-FTMS (NBA-NaI) *m/z* 416.2632 ($C_{25}H_{37}NO_2S$ + H^+ requires 416.2618).

1-[5-(3-Furyl)oxazol-2-yl]-1-oxo-9(*Z*)-octadecene. (159)

5-(3-Furyl)oxazole. This material was prepared from 3-furaldehyde using the procedure described for 5-(thiazol-2-yl)oxazole. Column chromatography (SiO_2, 2.5 x 12 cm, 10% Et_2O-hexanes) afforded 5-(3-furyl)oxazole (212 mg, 1.57 mmol, 16%) a yellow oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.85 (s, 1H), 7.48 (s, 1H), 7.44 (d, 1H, *J* = 1.8 Hz), 7.12 (s, 1H), 6.62 (d, 1H, *J* = 1.8 Hz).

1-[5-(3-Furyl)oxazol-2-yl]-1-oxo-9(*Z*)-octadecene. (159) This material was prepared from 5-(3-furyl)oxazole using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 5% Et_2O-hexanes) afforded **159** (54.8 mg, 0.137 mmol, 21%) a pale yellow oil: MALDI-FTMS (NBA-NaI) *m/z* 400.2848 ($C_{25}H_{37}NO_3$ + H^+ requires 400.2846).

1-(4-Phenyloxazol-2-yl)-1-oxo-9(*Z*)-octadecene. (162) A solution of 4-phenyloxazole (Giardina, et al. *J. Med. Chem.* **1997**, *40*, 1794-1807) (94.4 mg, 0.65 mmol, 1.0 equiv) in anhydrous THF (5.0 mL) at -78°C was treated dropwise with a solution of BuLi in hexanes (2.5 M, 0.29 mL, 0.725 mmol, 1.1 equiv) under N_2 and the resulting solution was stirred at -78°C for 20 min. A solution of $ZnCl_2$ in THF (0.5 M, 2.60 mL, 1.30 mmol, 2.0 equiv) was added to the mixture, and the mixture was warmed to 0°C. After stirring at 0°C for 45 min, CuI (107 mg, 0.56 mmol, 1.0 equiv) was added to the mixture. This was then stirred at 0°C for 10 min, a solution of 9(*Z*)-octadecen-1-oyl chloride (prepared from 385 mg of oleic

acid and 0.34 mL of oxalyl chloride, 1.30 mmol, 2.0 equiv) in anhydrous THF (3.0 mL) was added dropwise to the mixture, and the mixture was stirred at 0°C for an additional 1 h. The reaction mixture was diluted with a 1:1 mixture of hexanes and ethyl acetate (60 mL) and washed with 15% NH_4OH (2 x 30 mL), water (30 mL) and saturated aqueous NaCl (30 mL), successively. The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. Column chromatography (SiO_2, 2.5 x 12 cm, 3% Et_2O-hexanes) afforded **162** (115 mg, 0.282 mmol, 43%) as a colorless oil: MALDI-FTMS (NBA-NaI) *m/z* 432.2886 ($C_{27}H_{39}NO_2 + Na^+$ requires 432.2873).

1-(4-(Pyridin-2-yl)oxazol-2-yl)octadec-9-en-1-one. (163) A solution of 2-(oxazol-4-yl)pyridine (4 mg, 0.027 mmol) in anhydrous THF (1 mL) cooled to -75 °C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.030 mmol, 12 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 0.054 mmol, 22 mL) was added at -75 °C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.027 mmol, 5 mg) was added, and the solution was stirred for 10 min at 0°C. A separate flask was charged with oleic acid (2 equiv, 0.054 mmol, 15 mg) in anhydrous CH_2Cl_2 (0.5 mL), and to this solution cooled to 0°C under N_2 was added oxalyl chloride (5 equiv, 0.27 mmol, 34 mg, 24 mL). After stirring at rt for 2 h, the solution was concentrated under reduced pressure and dissolved in anhydrous THF (0.5 mL). The solution of oleoyl chloride was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 1.5 cm x 17.5 cm, 2% MeOH-CH_2Cl_2) afforded 1-(4-(pyridin-2-yl)oxazol-2-yl)octadec-9-en-1-one (**163**) (5 mg, 0.011 mmol, 42% yield) as a brown residue: ^1H NMR ($CDCl_3$, 250 MHz) d 8.66 (br d, J = 4.8 Hz, 1H), 7.90-7.68 (m, 4H), 5.40-5.25 (m, 2H), 3.10 (t, J = 7.4 Hz, 2H), 2.10-1.93 (m, 4H), 1.80-1.72 (m, 2H), 1.47-1.17 (m, 20H), 0.86 (br t, J = 6.6 Hz, 3H); IR ($CDCl_3$) u_{max} 2925, 2860, 1705, 1605, 1570, 1501, 1425, 1385 cm^{-1}; MALDI-FTMS (DHB) *m/z* 411.3003 ($C_{26}H_{38}N_2O_2 + H^+$ requires 411.3006).

1-(4-(Pyridin-3-yl)oxazol-2-yl)octadec-9-en-1-one. (164) A solution of 3-(oxazol-4-yl)pyridine (6 mg, 0.041 mmol) in anhydrous THF (1 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.045 mmol, 18 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 0.082 mmol, 33 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.041 mmol, 8 mg) was added, and the solution was stirred for 10 min at 0°C. A separate flask was charged with oleic acid (2 equiv, 0.082 mmol, 23 mg) in anhydrous CH_2Cl_2 (0.5 mL), and to this solution cooled to 0°C under N_2 was added oxalyl chloride (5 equiv, 0.41 mmol, 52 mg, 37 mL). After stirring at rt for 2 h, the solution was concentrated under reduced pressure and dissolved in anhydrous THF (0.5 mL). The solution of oleoyl chloride was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 1.5 cm x 17.5 cm, 2% MeOH-CH_2Cl_2) afforded 1-(4-(pyridin-3-yl)oxazol-2-yl)octadec-9-en-1-one (**164**) (4 mg, 0.009 mmol, 23% yield) as a brown residue: ^{1}H NMR ($CDCl_3$, 250 MHz) d 8.99 (br s, 1H), 8.65 (br d, J = 4.7 Hz, 1H), 8.04 (br d, J = 7.5 Hz, 1H), 7.86-7.54 (m, 2H), 5.41-5.26 (m, 2H), 3.10 (t, J = 7.4 Hz, 2H), 2.10-1.93 (m, 4H), 1.83-1.70 (m, 2H), 1.45-1.20 (m, 20H), 0.86 (br t, J = 6.6 Hz, 3H); IR ($CDCl_3$) u_{max} 2926, 2871, 1700, 1601, 1564, 1510, 1421, 1382 cm^{-1}; MALDI-FTMS (DHB) *m/z* 411.3012 ($C_{26}H_{38}N_2O_2$ + H^+ requires 411.3006).

1-(4-(Pyridin-4-yl)oxazol-2-yl)octadec-9-en-1-one. (165) A solution of 4-(oxazol-4-yl)pyridine (3 mg, 0.021 mmol) in anhydrous THF (1 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.023 mmol, 9 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 0.042 mmol, 17 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.021 mmol, 4 mg) was added, and the solution was stirred for 10 min at 0°C. A separate flask was charged with oleic acid (2 equiv, 0.042 mmol, 12 mg) in anhydrous CH_2Cl_2 (0.5 mL), and to this solution cooled to 0°C under N_2 was added oxalyl chloride (5 equiv, 0.21 mmol, 27 mg, 19 mL). After stirring at rt for 2 h, the solution was

concentrated under reduced pressure and dissolved in anhydrous THF (0.5 mL). The solution of oleoyl chloride was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 1.5 cm x 17.5 cm, 2% MeOH-CH_2Cl_2) afforded 1-(4-(pyridin-4-yl)oxazol-2-yl)octadec-9-en-1-one (**165**) (2 mg, 0.005 mmol, 24% yield) as a brown residue: ^1H NMR ($CDCl_3$, 250 MHz) d 8.75 (m, 2H), 7.70-7.61 (m, 3H), 5.42-5.27 (m, 2H), 3.09 (t, *J* = 7.4 Hz, 2H), 2.12-1.89 (m, 4H), 1.82-1.75 (m, 2H), 1.48-1.21 (m, 20H), 0.87 (br t, *J* = 6.8 Hz, 3H); IR ($CDCl_3$) u_{max} 2926, 2873, 1702, 1612, 1559, 1512, 1425, 1380 cm^{-1}; MALDI-FTMS (DHB) *m/z* 411.2997 ($C_{26}H_{38}N_2O_2 + H^+$ requires 411.3006).

1-(5-(Pyridin-2-yl)oxazol-2-yl)octadecan-1-one. (182) A solution of 2-(oxazol-5-yl)pyridine (113 mg, 0.77 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.85 mmol, 0.34 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.54 mmol, 3.1 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.77 mmol, 147 mg) was added, and the solution was stirred for 10 min at 0°C. A separate flask was charged with stearic acid (2 equiv, 1.54 mmol, 440 mg) in anhydrous CH_2Cl_2 (4.2 mL), and to this solution cooled to 0°C under N_2 was added oxalyl chloride (5 equiv, 7.7 mmol, 0.98 g, 0.68 mL). After stirring at rt for 2 h, the solution was concentrated under reduced pressure and dissolved in anhydrous THF (1.5 mL). The solution of stearoyl chloride was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x 17.5 cm, 20% EtOAc-hexanes) afforded 1-(5-(pyridin-2-yl)oxazol-2-yl)octadecan-1-one (**182**) (97 mg, 0.24 mmol, 31% yield) as a white powder: mp 86-87°C; ^1H NMR ($CDCl_3$, 250 MHz) d 8.66 (br d, *J* = 5.4 Hz, 1H), 7.89-7.76 (m, 3H), 7.34-7.27 (m, 1H), 3.10 (t, *J* = 7.7 Hz, 2H), 1.82-1.74 (m, 2H), 1.44-1.19 (m, 28H), 0.87

(br t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 188.6, 157.4, 153.2, 150.1 (2C), 137.1, 126.8, 124.1, 120.3, 39.2, 31.9, 29.7 (5C), 29.6 (2C), 29.6, 29.4, 29.3 (2C), 29.2, 24.0, 22.7, 14.1; IR (KBr) u_{max} 2942, 2871, 1701, 1601, 1429, 1376 cm^{-1}; MALDI-FTMS (DHB) *m/z* 413.3170 ($C_{26}H_{40}N_2O_2$ + H^+ requires 713.3162).

1-(5-(Pyridin-2-yl)oxazol-2-yl)hexadecan-1-one. (183) A solution of 2-(oxazol-5-yl)pyridine (95 mg, 0.65 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.72 mmol, 0.29 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.30 mmol, 2.6 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.65 mmol, 124 mg) was added, and the solution was stirred for 10 min at 0°C. Palmitoyl chloride (2 equiv, 1.3 mmol, 357 mg, 0.39 mL) was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x 17.5 cm, 20% EtOAc-hexanes) afforded 1-(5-(pyridin-2-yl)oxazol-2-yl)hexadecan-1-one (**183**) (103 mg, 0.27 mmol, 42% yield) as an off-white powder: mp 78-80°C; ^1H NMR ($CDCl_3$, 250 MHz) d 8.66 (br d, J = 5.1 Hz, 1H), 7.88-7.76 (m, 3H), 7.34-7.27 (m, 1H), 3.10 (t, J = 7.3 Hz, 2H), 1.83-1.70 (m, 2H), 1.24 (br s, 24H), 0.87 (br t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 188.6, 157.4, 153.2, 150.1, 146.3, 137.0, 126.8, 124.1, 120.4, 39.2, 31.9, 29.6 (2C), 29.6 (2C), 29.4 (2C), 29.3 (3C), 29.2 24.0, 22.7, 14.1; IR (KBr) u_{max} 2935, 2847, 1699, 1605, 1425, 1381 cm^{-1}; MALDI-FTMS (DHB) *m/z* 385.2841 ($C_{24}H_{36}N_2O_2$ + H^+ requires 385.2849).

1-(5-(Pyridin-2-yl)oxazol-2-yl)tetradecan-1-one. (184) A solution of 2-(oxazol-5-yl)pyridine (97 mg, 0.66 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.73 mmol, 0.29 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.32 mmol, 2.7 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.66 mmol, 126 mg) was added, and the solution was stirred for 10 min at 0°C. A separate flask was charged with myristic acid (2 equiv, 1.32 mmol, 303 mg) in anhydrous CH_2Cl_2 (4.2

mL), and to this solution cooled to 0°C under N_2 was added oxalyl chloride (5 equiv, 6.6 mmol, 0.84 g, 0.58 mL). After stirring at rt for 2 h, the solution was concentrated under reduced pressure and dissolved in anhydrous THF (1.5 mL). The solution of myristoyl chloride was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x 17.5 cm, 20% EtOAc-hexanes) afforded 1-(5-(pyridin-2-yl)oxazol-2-yl)tetradecan-1-one (**184**) (102 mg, 0.29 mmol, 44% yield) as a white powder: mp 79-80°C; ^1H NMR ($CDCl_3$, 250 MHz) d 8.65 (br d, *J* = 4.8 Hz, 1H), 7.89-7.75 (m, 3H), 7.34-7.25 (m, 1H), 3.10 (t, *J* = 7.3 Hz, 2H), 1.80-1.70 (m, 2H), 1.43-1.18 (m, 20H), 0.86 (br t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 188.6, 157.4, 153.2, 150.1 (2C), 146.4, 137.1, 126.8, 124.1, 120.3, 39.1, 31.9, 29.6 (2C), 29.6, 29.4, 29.3 (2C), 29.2, 24.0, 22.7, 14.1; IR (KBr) u_{max} 2960, 2878, 1705, 1598, 1426, 1387 cm^{-1}; MALDI-FTMS (DHB) *m/z* 357.2536 ($C_{22}H_{32}N_2O_2 + H^+$ requires 357.2536).

1-(5-(Pyridin-2-yl)oxazol-2-yl)dodecan-1-one. (185) A solution of 2-(oxazol-5-yl)pyridine (102 mg, 0.70 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.77 mmol, 0.31 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.40 mmol, 2.8 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.70 mmol, 133 mg) was added, and the solution was stirred for 10 min at 0°C. Lauroyl chloride (2 equiv, 1.4 mmol, 306 mg, 0.32 mL) was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x 17.5 cm, 20% EtOAc-hexanes) afforded 1-(5-(pyridin-2-yl)oxazol-2-yl)dodecan-1-one (**185**) (122 mg, 0.37 mmol, 53% yield) as an off-white powder: mp 73-74°C; ^1H NMR ($CDCl_3$, 250 MHz) d 8.65 (br d, *J* = 4.0 Hz, 1H), 7.89-7.75 (m, 3H), 7.34-7.25 (m, 1H), 3.09 (t, *J* = 7.7 Hz, 2H), 1.83-1.69 (m, 2H), 1.41-1.19 (m, 16H), 0.86 (br t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 62.5 MHz) d 188.6, 153.2, 150.1 (2C), 146.3, 137.1, 126.8, 124.1, 120.3, 39.1, 31.9, 29.6 (2C), 29.4, 29.3, 29.2 (2C), 24.0, 22.7, 14.1; IR (KBr) u_{max} 2929, 2857, 1704, 1609, 1415, 1378 cm^{-1}; MALDI-FTMS (DHB) *m/z* 329.2214 ($C_{20}H_{28}N_2O_2$ + H^+ requires 329.2223).

1-(5-(Pyridin-2-yl)oxazol-2-yl)decan-1-one. (**187**) A solution of 2-(oxazol-5-yl)pyridine (100 mg, 0.68 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.75 mmol, 0.30 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.40 mmol, 2.8 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.68 mmol, 130 mg) was added, and the solution was stirred for 10 min at 0°C. Decanoyl chloride (2 equiv, 1.4 mmol, 270 mg, 0.29 mL) was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x 17.5 cm, 20% EtOAc-hexanes) afforded 1-(5-(pyridin-2-yl)oxazol-2-yl)decan-1-one (**187**) (80 mg, 0.27 mmol, 40% yield) as a light brown powder: mp 56-57°C; ^1H NMR ($CDCl_3$, 250 MHz) d 8.69-8.62 (m, 1H), 7.87-7.75 (m, 3H), 7.33-7.25 (m, 1H), 3.08 (t, *J* = 7.7 Hz, 2H), 1.81-1.69 (m, 2H), 1.41-1.19 (m, 12H), 0.86 (br t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 188.5, 157.3, 153.1, 150.0, 146.2, 136.9, 127.8, 124.1, 120.3, 39.1, 31.8, 29.4, 29.3, 29.2, 29.1, 24.0, 22.6, 14.0; IR (KBr) u_{max} 2930, 2845, 1697, 1601, 1422, 1380 cm^{-1}; MALDI-FTMS (DHB) *m/z* 300.1911 ($C_{18}H_{24}N_2O_2$ + H^+ requires 301.1910).

1-(5-(Pyridin-2-yl)oxazol-2-yl)nonan-1-one. (**188**) A solution of 2-(oxazol-5-yl)pyridine (117 mg, 0.80 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.88 mmol, 0.35 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.60 mmol, 3.2 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.80 mmol, 152 mg) was added, and the solution was stirred for 10 min at 0°C. A separate flask was charged with nonanoic acid (2 equiv, 1.60 mmol, 253 mg, 0.28 mL) in anhydrous

CH_2Cl_2 (4.2 mL), and to this solution cooled to 0°C under N_2 was added oxalyl chloride (5 equiv, 8.0 mmol, 1.02 g, 0.70 mL). After stirring at rt for 2 h, the solution was concentrated under reduced pressure and dissolved in anhydrous THF (1.5 mL). The solution of nonanoyl chloride was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x 17.5 cm, 20% EtOAc-hexanes) afforded 1-(5-(pyridin-2-yl)oxazol-2-yl)nonan-1-one (**188**) (94 mg, 0.33 mmol, 41% yield) as a light brown powder: mp 56-57°C; ^1H NMR ($CDCl_3$, 250 MHz) d 8.61 (br d, J = 4.4 Hz, 1H), 7.84-7.71 (m, 3H), 7.29-7.22 (m, 1H), 3.05 (t, J = 7.3 Hz, 2H), 1.79-1.66 (m, 2H), 1.42-1.16 (m, 10H), 0.88-0.77 (m, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 188.4, 157.3, 153.1, 150.0, 146.2, 137.0, 126.8, 124.0, 120.3, 39.0, 31.7, 29.2, 29.0, 24.0, 23.9, 22.5, 14.0; IR (KBr) u_{max} 2922, 2856, 1705, 1697, 1600, 1420, 1381 cm^{-1}; MALDI-FTMS (DHB) *m/z* 287.1744 ($C_{17}H_{22}N_2O_2$ + H^+ requires 287.1754).

1-(5-(Pyridin-2-yl)oxazol-2-yl)octan-1-one. (189) A solution of 2-(oxazol-5-yl)pyridine (111 mg, 0.76 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.84 mmol, 0.33 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.52 mmol, 3.0 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.76 mmol, 145 mg) was added, and the solution was stirred for 10 min at 0°C. A separate flask was charged with octanoic acid (2 equiv, 1.52 mmol, 219 mg, 0.24 mL) in anhydrous CH_2Cl_2 (4.2 mL), and to this solution cooled to 0°C under N_2 was added oxalyl chloride (5 equiv, 7.6 mmol, 0.96 g, 0.66 mL). After stirring at rt for 2 h, the solution was concentrated under reduced pressure and dissolved in anhydrous THF (1.5 mL). The solution of octanoyl chloride was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x

17.5 cm, 20% EtOAc-hexanes) afforded 1-(5-(pyridin-2-yl)oxazol-2-yl)octan-1-one (**189**) (107 mg, 0.39 mmol, 52% yield) as a light brown powder: mp 56°C; ^{1}H NMR ($CDCl_3$, 250 MHz) d 8.63 (br d, *J* = 4.8 Hz, 1H), 7.85-7.74 (m, 3H), 7.28 (br t, *J* = 5.1 Hz, 1H), 3.08 (t, *J* = 7.3 Hz, 2H), 1.84-1.67 (m, 2H), 1.47-1.17 (m, 8H), 0.85 (br t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 188.5, 157.3, 153.1, 150.0, 146.2, 137.0, 127.8, 124.1, 120.3, 39.1, 31.6, 29.0, 28.9, 24.0, 22.5, 14.0; IR (KBr) u_{max} 2926, 2849, 1694, 1601, 1499, 1470, 1426, 1382 cm^{-1}; MALDI-FTMS (DHB) *m/z* 273.1595 ($C_{16}H_{20}N_2O_2$ + H^+ requires 273.1597).

1-(5-(Pyridin-2-yl)oxazol-2-yl)heptan-1-one. (190) A solution of 2-(oxazol-5-yl)pyridine (112 mg, 0.77 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.85 mmol, 0.34 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.58 mmol, 3.1 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.77 mmol, 146 mg) was added, and the solution was stirred for 10 min at 0°C. A separate flask was charged with heptanoic acid (2 equiv, 1.55 mmol, 202 mg, 0.22 mL) in anhydrous CH_2Cl_2 (4.2 mL), and to this solution cooled to 0°C under N_2 was added oxalyl chloride (5 equiv, 7.8 mmol, 0.99 g, 0.68 mL). After stirring at rt for 2 h, the solution was concentrated under reduced pressure and dissolved in anhydrous THF (1.5 mL). The solution of heptanoyl chloride was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x 17.5 cm, 20% EtOAc-hexanes) afforded 1-(5-(pyridin-2-yl)oxazol-2-yl)heptan-1-one (**190**) (97 mg, 0.38 mmol, 49% yield) as a light brown powder: mp 52°C; ^{1}H NMR ($CDCl_3$, 250 MHz) d 8.63 (br d, *J* = 4.8 Hz, 1H), 7.85-7.74 (m, 3H), 7.31-7.25 (m, 1H), 3.08 (t, *J* = 7.7 Hz, 2H), 1.78-1.69 (m, 2H), 1.44-1.22 (m, 6H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 188.5, 157.3, 153.2, 150.0, 146.3, 137.0, 126.8, 124.1, 120.3, 39.1, 31.4, 28.8, 23.9, 22.4, 14.0; IR (KBr) u_{max} 2933, 2847, 1698, 1604, 1430, 1387 cm^{-1}; MALDI-FTMS (DHB) *m/z* 259.1436 ($C_{15}H_{18}N_2O_2$ + H^+ requires 259.1441).

1-(5-(Pyridin-2-yl)oxazol-2-yl)hexan-1-one. (191) A solution of 2-(oxazol-5-yl)pyridine (116 mg, 0.79 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.87 mmol, 0.35 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.58 mmol, 3.2 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.79 mmol, 151 mg) was added, and the solution was stirred for 10 min at 0°C. A separate flask was charged with hexanoic acid (2 equiv, 1.58 mmol, 186 mg, 0.20 mL) in anhydrous CH_2Cl_2 (4.2 mL), and to this solution cooled to 0°C under N_2 was added oxalyl chloride (5 equiv, 8.0 mmol, 1.02 g, 0.70 mL). After stirring at rt for 2 h, the solution was concentrated under reduced pressure and dissolved in anhydrous THF (1.5 mL). The solution of hexanoyl chloride was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x 17.5 cm, 20% EtOAc-hexanes) afforded 1-(5-(pyridin-2-yl)oxazol-2-yl)hexan-1-one (**191**) (50 mg, 0.20 mmol, 25% yield) as a light brown powder: mp 49-50.5°C; ^{1}H NMR ($CDCl_3$, 250 MHz) d 8.64 (br d, *J* = 3.9 Hz, 1H), 7.85-7.75 (m, 3H), 7.32-7.26 (m, 1H), 3.09 (t, *J* = 7.7 Hz, 2H), 1.82-1.70 (m, 2H), 1.40-1.31 (m, 4H), 0.89 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 181.5, 150.3, 146.2, 143.0, 139.3, 130.0, 119.8, 117.0, 113.3, 32.0, 24.2, 16.6, 15.3, 6.8; IR (KBr) u_{max} 2957, 2872, 1700, 1677, 1603, 1426, 1387 cm^{-1}; MALDI-FTMS (DHB) *m/z* 245.1284 ($C_{14}H_{16}N_2O_2 + H^+$ requires 245.1284).

1-(5-(Pyridin-2-yl)oxazol-2-yl)pentan-1-one. (192) A solution of 2-(oxazol-5-yl)pyridine (116 mg, 0.79 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.87 mmol, 0.35 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.58 mmol, 3.2 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.79 mmol, 151 mg) was added, and the solution was stirred for 10 min at 0°C. A separate flask was charged with valeric acid (2 equiv, 1.58 mmol, 161 mg, 0.17 mL) in anhydrous CH_2Cl_2 (4.2 mL), and to this solution cooled to 0°C under N_2 was added oxalyl

chloride (5 equiv, 7.89 mmol, 1.00 g, 0.69 mL). After stirring at rt for 2 h, the solution was concentrated under reduced pressure and dissolved in anhydrous THF (1.5 mL). The solution of valeryl chloride was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x 17.5 cm, 20% EtOAc-hexanes) afforded 1-(5-(pyridin-2-yl)oxazol-2-yl)pentan-1-one (**192**) (43 mg, 0.19 mmol, 24% yield) as a light brown powder: mp 36-37°C; ^1H NMR ($CDCl_3$, 250 MHz) d 8.68-8.66 (m, 1H), 7.89-7.81 (m, 3H), 7.34-7.29 (m, 1H), 3.12 (t, *J* = 7.7 Hz, 2H), 1.83-1.71 (m, 2H), 1.48-1.39 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 188.5, 162.1, 157.6, 150.0, 137.1, 127.9, 126.8, 124.1, 120.3, 38.9, 26.0, 22.2, 13.8; IR (KBr) u_{max} 2954, 2926, 2862, 1700, 1690, 1602, 1472, 1427, 1381, cm^{-1}; MALDI-FTMS (DHB) *m/z* 253.0950 ($C_{13}H_{14}N_2O_2 + Na^+$ requires 253.0947).

1-[5-(Pyridin-2-yl)oxazol-2-yl]butan-1-one. (193) A solution of 2-(oxazol-5-yl)pyridine (98 mg, 0.67 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.74 mmol, 0.3 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.34 mmol, 2.7 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.67 mmol, 128 mg) was added, and the solution was stirred for 10 min at 0°C. Butyryl chloride (2.0 equiv, 1.34 mmol, 143 mg, 0.14 mL) was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x 17.5 cm, 20% EtOAc-hexanes) afforded 1-(5-(pyridin-2-yl)oxazol-2-yl)butan-1-one (**193**) (68 mg, 0.31 mmol, 46% yield) as a light brown powder: mp 54-55°C; ^1H NMR ($CDCl_3$, 250 MHz) d 8.65-8.62 (m, 1H), 7.85-7.78 (m, 3H), 7.31-7.26 (m, 1H), 3.07 (t, *J* = 7.3 Hz, 2H), 1.87-1.72 (m, 2H), 1.00 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 188.4, 162.0, 157.3, 150.1, 146.3, 136.9, 126.8, 124.1, 120.3, 40.9, 17.5, 13.5; IR

(KBr) u_{max} 2963, 2933, 2872, 1675, 1469, 1426, 1387, 1227 cm^{-1}; MALDI-FTMS (DHB) *m/z* 217.0968 ($C_{12}H_{12}N_2O_2$ + H^+ requires 217.0971).

1-[5-(Pyridin-2-yl)oxazol-2-yl]propan-1-one. (194) A solution of 2-(oxazol-5-yl)pyridine (98 mg, 0.67 mmol) in anhydrous THF (5 mL) cooled to -75°C under N_2 was treated with *n*-BuLi (2.5 M in hexanes, 1.1 equiv, 0.74 mmol, 0.3 mL), and stirred for 20 min. $ZnCl_2$ (0.5 M in THF, 2.0 equiv, 1.34 mmol, 2.7 mL) was added at -75°C, and stirred for 45 min at 0°C. CuI (1.0 equiv, 0.67 mmol, 128 mg) was added, and the solution was stirred for 10 min at 0°C. Propionyl chloride (2.0 equiv, 1.34 mmol, 124 mg, 0.12 mL) was added and the solution was stirred for 1 h at 0°C. The reaction was diluted with EtOAc (10 mL), and washed with 15% aqueous NH_4OH (1 x 10 mL), H_2O (1 x 10 mL), and saturated aqueous NaCl (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 2.5 cm x 17.5 cm, 20% EtOAc-hexanes) afforded 1-[5-(pyridin-2-yl)oxazol-2-yl]propan-1-one (**194**) (89 mg, 0.44 mmol, 65% yield) as a light brown powder: mp 65-67°C; ^1H NMR ($CDCl_3$, 250 MHz) d 8.65-8.62 (m, 1H), 7.86-7.75 (m, 3H), 7.31-7.26 (m, 1H), 3.18-3.08 (m, 2H), 1.29-1.21 (m, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) d 188.8, 161.9, 157.2, 150.1, 146.3, 136.9, 126.8, 124.0, 120.3, 32.5, 7.8; IR (KBr) u_{max} 2935, 2862, 1699, 1471, 1426, 1377 cm^{-1}; MALDI-FTMS (DHB) *m/z* 203.0818 ($C_{11}H_{10}N_2O_2$ + H^+ requires 203.0815).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-2-phenylethane. (195) This material was prepared from 5-(2-pyridyl)oxazole and phenylacetic acid using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **195** (5.7 mg, 0.022 mmol, 3%) as a yellow oil: MALDI-FTMS (NBA-NaI) *m/z* 265.0963 ($C_{16}H_{12}N_2O_2$ + H^+ requires 265.0971).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-3-phenylpropane. (196) This material was prepared from 5-(2-pyridyl)oxazole and hydrocinnamic acid using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **196** (46.9 mg, 0.169 mmol, 26%) a yellow crystalline powder:

mp 67.0-70.0°C; MALDI-FTMS (NBA-NaI) *m/z* 279.1120 ($C_{17}H_{14}N_2O_2$ + H^+ requires 279.1128).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-4-phenylbutane. (197) This material was prepared from 5-(2-pyridyl)oxazole and 4-phenylbutyric acid using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **197** (28.3 mg, 0.097 mmol, 15%) a yellow crystalline powder: mp 69.0-72.0°C; MALDI-FTMS (NBA-NaI) *m/z* 293.1287 ($C_{18}H_{16}N_2O_2$ + H^+ requires 293.1284).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-5-phenylpentane. (198) This material was prepared from 5-(2-pyridyl)oxazole and 5-phenylpentanoic acid using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **198** (39.5 mg, 0.129 mmol, 20%) a yellow crystalline powder: mp 49.0-51.0°C; MALDI-FTMS (NBA-NaI) *m/z* 307.1440 ($C_{19}H_{18}N_2O_2$ + H^+ requires 307.1441).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-6-phenylhexane. (199) This material was prepared from 5-(2-pyridyl)oxazole and 6-phenylhexanoic acid using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **199** (50.0 mg, 0.156 mmol, 24%) a pale yellow crystalline powder: mp 43.5-45.5°C; MALDI-FTMS (NBA-NaI) *m/z* 321.1607 ($C_{20}H_{20}N_2O_2$ + H^+ requires 321.1597).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-7-phenylheptane. (200) This material was prepared from 5-(2-pyridyl)oxazole and 7-phenylheptanoic acid using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **200** (70.9 mg, 0.212 mmol, 33%) a pale yellow crystalline powder: mp 45.0-48.0°C; MALDI-FTMS (NBA-NaI) *m/z* 335.1756 ($C_{21}H_{22}N_2O_2$ + H^+ requires 335.1754).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-8-phenyloctane. (201) This material was prepared from 5-(2-pyridyl)oxazole and 8-phenyloctanoic acid using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **201** (62.6 mg, 0.180 mmol, 28%) a pale yellow crystalline powder: mp 72.0-73.0°C; MALDI-FTMS (NBA-NaI) *m/z* 349.1905 ($C_{22}H_{24}N_2O_2 + H^+$ requires 349.1910).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-9-phenylnonane. (202) This material was prepared from 5-(2-pyridyl)oxazole and 9-phenylnonanoic acid (Kiuchi, F.; et al. *Chem. Pharm. Bull.* **1997**, *45*, 685-696) using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **202** (88.9 mg, 0.245 mmol, 35%) a pale yellow crystalline powder: mp 39.0-41.0°C; MALDI-FTMS (NBA-NaI) *m/z* 363.2058 ($C_{23}H_{26}N_2O_2 + H^+$ requires 363.2067).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-9-decene. (203) This material was prepared from 5-(2-pyridyl)oxazole and 9-decenoic acid using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **203** (64.5 mg, 0.216 mmol, 33%) a pale yellow crystalline powder: mp 55.0-57.0°C; MALDI-FTMS (NBA-NaI) *m/z* 299.1748 ($C_{18}H_{22}N_2O_2 + H^+$ requires 299.1754).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-9-decyne. (204) This material was prepared from 5-(2-pyridyl)oxazole and 9-decynoic acid using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **204** (67.9 mg, 0.229 mmol, 47%) a colorless crystalline powder: mp 64.5-65.5°C; MALDI-FTMS (NBA-NaI) *m/z* 297.1589 ($C_{18}H_{20}N_2O_2 + H^+$ requires 297.1597).

1-Oxo-1-[5-(2-pyridyl)oxazol-2-yl]-9-octadecyne. (205) This material was prepared from 5-(2-pyridyl)oxazole and stearolic acid using the procedure described for **162**. Column chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **205** (75.7 mg, 0.185 mmol, 29%) a colorless crystalline

powder: mp 41.0°C; MALDI-FTMS (NBA-NaI) *m/z* 409.2850 ($C_{26}H_{36}N_2O_2 + H^+$ requires 409.2849).

1-(4,5-Diphenyloxazol-2-yl)-1-oxo-9(Z)-octadecene. (212)

4,5-Diphenyloxazole. A mixture of α-bromo-α-phenylacetophenone (densyl bromide, 5.53 g, 20.10 mmol, 1.0 equiv), ammonium formate (4.4 g, 69.8 mmol, 3.5 equiv) and formic acid (96%, 21.3 mL) were warmed at reflux for 2.5 h. The mixture was cooled to room temperature, added dropwise to ice-cooled water (70 mL), and then the solution was made basic with the addition of 30% aqueous NaOH. It was extracted with ether (200 mL then 100 mL), and the separated organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. Chromatography (SiO_2, 2.5 x 12 cm, 2% EtOAc-hexanes) afforded 4,5-diphenyloxazole (752 mg, 3.40 mmol, 17%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.96 (s, 1H), 7.72-7.59 (m, 4H), 7.45-7.33 (m, 6H).

1-(4,5-Diphenyloxazol-2-yl)-1-oxo-9(*Z*)-octadecene. This material was prepared from 4,5-diphenyloxazole using the procedure described for **162.** Column chromatography (SiO_2, 2.5 x 12 cm, 2% Et_2O-hexanes) afforded **212** (33.3 mg, 0.069 mmol, 11%) as a yellow oil: MALDI-FTMS (NBA-NaI) *m/z* 508.3177 ($C_{33}H_{43}NO_2 + Na^+$ requires 508.3186).

1-(4,5-Dimethyloxazol-2-yl)-1-oxo-9(*Z*)-octadecene. (213)

4,5-Dimethyloxazole. (Theilig, G. *Chem. Ber.* **1953**, *86*, 96-109) A mixture of 3-chloro-2-butanone (2.50 g, 23.46 mmol, 1.0 equiv), tetrabutylammonium bromide (152 mg, 0.47 mmol, 0.02 equiv) and formamide (7.5 mL) were heated at 100°C for 6 h. The product was distilled from the mixture under atmospheric pressure to afford 4,5-dimethyloxazole (bath temp. 150-170°C, 796 mg, 8.20 mmol, 35%) as a colorless oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.66 (s, 1H), 2.23 (s, 3H), 2.09 (s, 3H).

1-(4,5-Dimethyloxazol-2-yl)-1-oxo-9(*Z*)-octadecene. This material was prepared from 4,5-dimethyloxazole using the procedure described for **162.** Column chromatography (SiO_2, 2.5 x 12 cm, 5% Et_2O-hexanes) afforded **213** (106

Column chromatography (SiO_2, 2.5 x 12 cm, 5% Et_2O-hexanes) afforded **213** (106 mg, 0.293 mmol, 45%) as a pale yellow oil: MALDI-FTMS (NBA-NaI) *m/z* 362.3049 ($C_{23}H_{39}NO_2 + H^+$ requires 362.3054).

1-Hydroxy-1-[5-(2-pyridyl)oxazol-2-yl]-9(*Z*)-octadecene. Sodium borohydride (1.8 mg, 0.048 mmol) was added to a solution of 1-oxo-1-[5-(2-pyridyl)oxazol-2-yl]-9(Z)-octadecene **(143)** (13.0 mg, 0.032 mmol) in a 1:1 mixture of methanol and THF (3.0 mL) at 0°C. After stirring at 0°C for 20 min, saturated aqueous NaCl was added to the mixture, and the mixture was extracted with ethyl acetate (40 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. Chromatography (SiO_2, 1.5 x 12 cm, 50% EtOAc-hexanes) afforded **26** (7.2 mg, 0.017 mmol, 55%) as a colorless solid: mp. 37.5-39.5°C; MALDI-FTMS (NBA-NaI) *m/z* 413.3164 ($C_{26}H_{40}N_2O_2 + H^+$ requires 413.3162).

1-[5-(2-Pyridyl)oxazol-2-yl]-9(*Z*)-octadecene. Triphenylphosphine (69.3 mg, 0.264 mmol, 5.0 equiv) and carbon tetrabromide (87.6 mg, 0.264 mmol, 5.0 equiv) were added to a solution of 1-hydroxy-1-[5-(2-pyridyl)oxazol-2-yl]-9(*Z*)-octadecene (**26**, 21.8 mg, 0.053 mmol) in dichloromethane (2.0 mL) at 0°C (A similar reaction was reported: Bohlmann, F.; et al. *Chem. Ber.* **1976**, *109*, 1586-1588). After stirring at 0°C for 30 min, the mixture was diluted with dichloromethane (50 mL) and washed with water (25 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. Chromatography (SiO_2, 1.5 x 12 cm, 20% EtOAc-hexanes) afforded **27** (2.1 mg, 0.0053 mmol, 10%) as a pale yellow oil: MALDI-FTMS (NBA-NaI) *m/z* 397.3209 ($C_{26}H_{40}N_2O + H^+$ requires 397.3213).

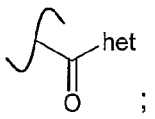
What is claimed is:

1. An inhibitor of fatty acid amide hydrolase represented by the following formula:

A-B-C

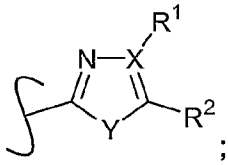
wherein A is an inhibition subunit, B is a linkage subunit, and C is a binding subunit and wherein:

the inhibition subunit A is an α-keto heterocyclic pharmacophore for inhibiting the fatty acid amide hydrolase, the α-keto heterocyclic pharmacophore being represented by the formula:



;

wherein "het" is represented by the following structure:



; wherein:

X is selected from the group consisting of carbon and nitrogen;

Y is selected from the group consisting of oxygen and sulfur;

R^1 and R^2 are radicals independently selected from the group consisting of hydrogen, C1-C6 alkyl, aromatic ring, and heteroaromatic ring;

with the following provisos:

R^1 and R^2 cannot both be hydrogen; and

if X is nitrogen, R^1 is absent;

the linkage subunit **B** is a chain for linking the inhibition subunit **A** and

the binding subunit **C** and for enabling the binding subunit **C** to bind to the binding region on the fatty acid amide hydrolase, the chain having a linear skeleton of between 3 and 9 atoms selected from the group consisting of carbon, oxygen, sulfur, and nitrogen, the linear skeleton having a first end and a second end, the first end being covalently bonded to the α-keto group of **A**,

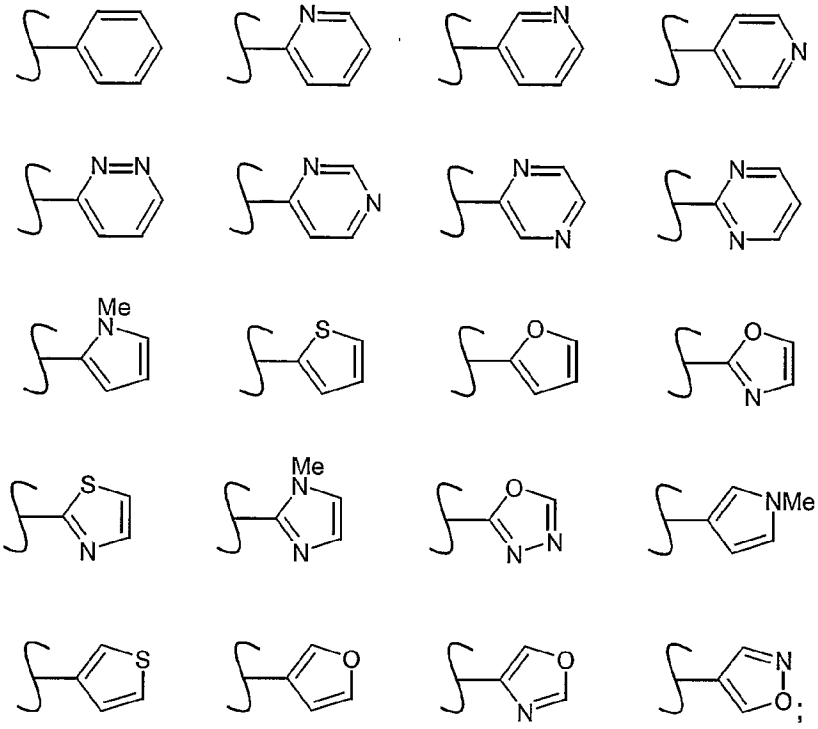
with the following proviso:

if the first end of said chain is an α-carbon with respect to the α-keto group of the inhibition subunit **A**, then the α-carbon is optionally mono- or bis-functionalized with substituents selected from the group consisting of fluoro, chloro, hydroxyl, alkoxy, trifluoromethyl, and alkyl; and

the binding subunit **C** is a π-bond containing radical having a π-unsaturation and being selected from a group consisting of aryl, alkenyl, alkynyl, and ring structures having at least one unsaturation, with or without one or more heteroatoms, the binding subunit **C** being covalently bonded to the second end of the linkage subunit **B**, the π-unsaturation within the π-bond containing radical being separated from the α-keto group of **A** by a sequence of no less than 3 and no more than 9 atoms bonded sequentially to one another, inclusive of the linear skeleton for enabling the π-unsaturation to bind to the binding region of the fatty acid amide hydrolase while the inhibition subunit **A** inhibits the fatty acid amide hydrolase;

with a proviso that **C** is optionally C1-C10 alkyl.

2. An inhibitor of fatty acid amide hydrolase according to claim 1 wherein R^1 and R^2 are radicals independently selected from the group consisting of hydrogen, C1-C6 alkyl, and radicals represented by the following structures:



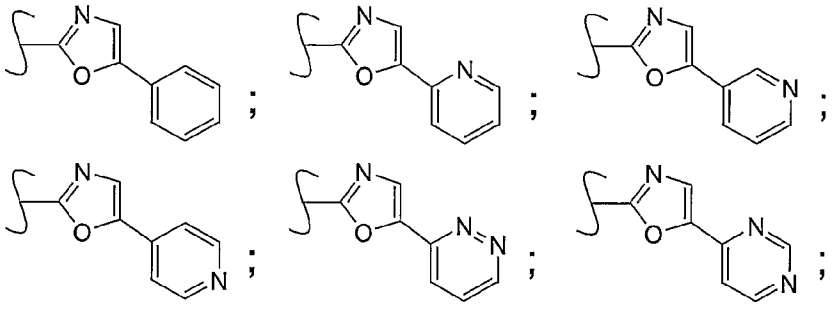
with the following provisos:

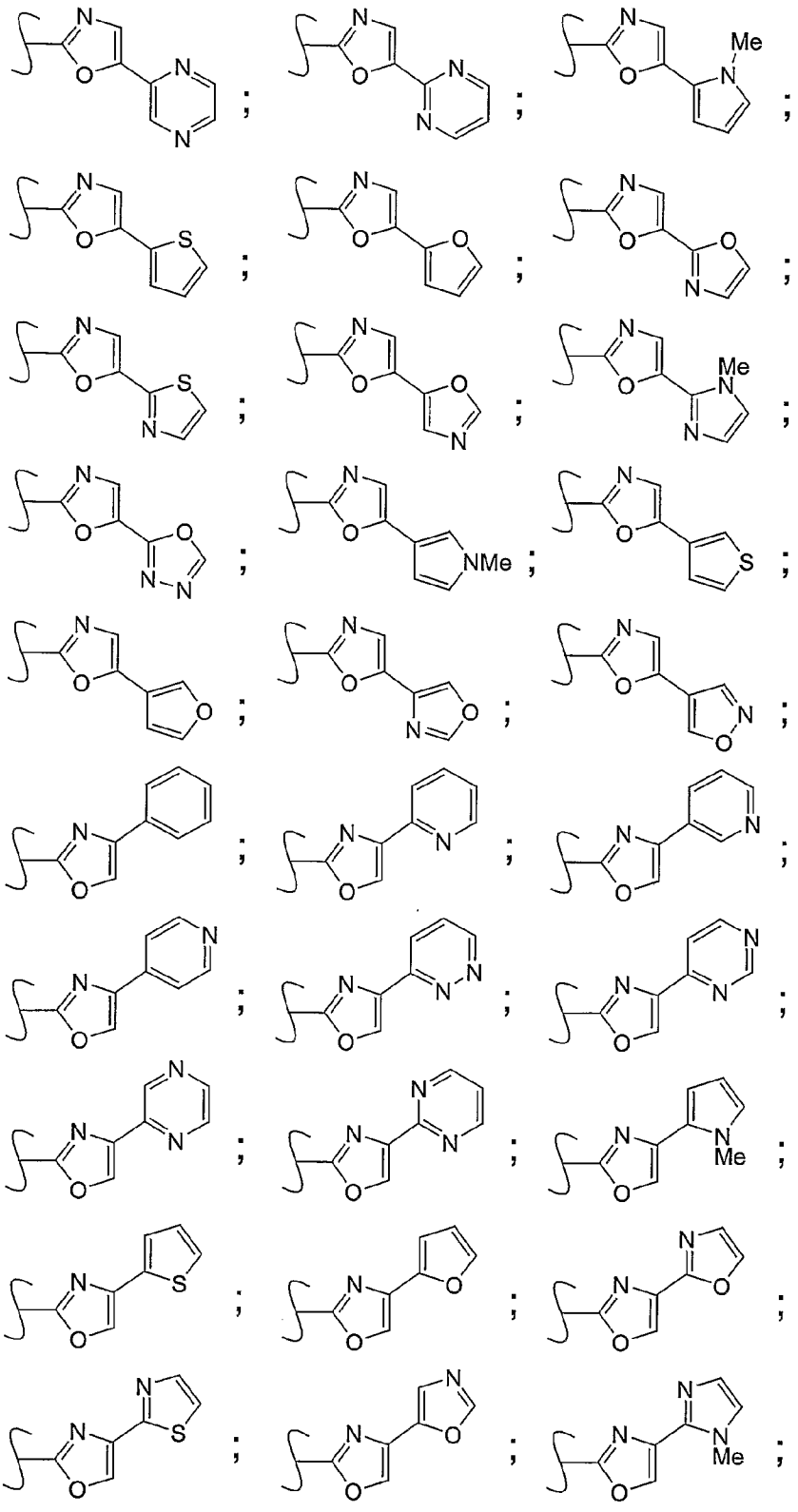
R^1 and R^2 cannot both be hydrogen; and

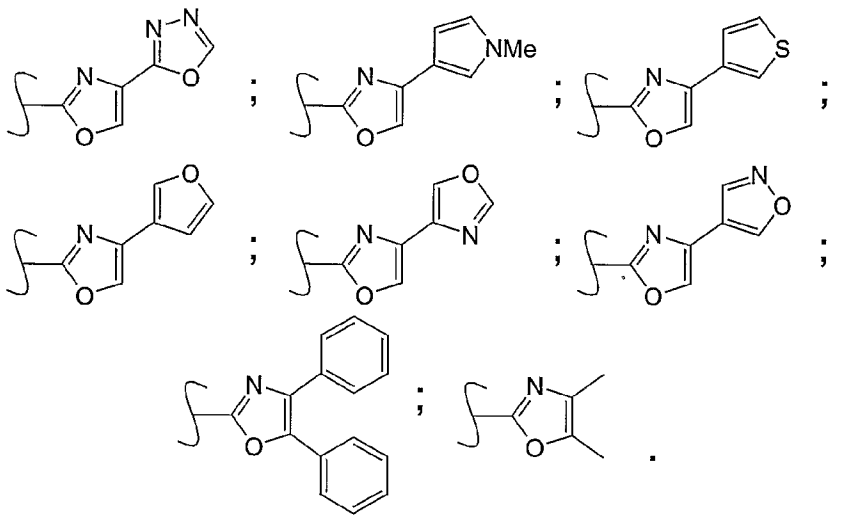
if X is nitrogen, R^1 is absent.

3. An inhibitor of fatty acid amide hydrolase according to claim 2 wherein:

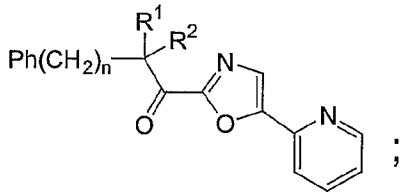
"het" of the α-keto heterocyclic pharmacophore is selected from the following group:







4. An inhibitor of fatty acid amide hydrolase according to claim 3 wherein the inhibitor is represented by the following structure:



wherein

R^1 and R^2 are independently selected from the group consisting of hydrogen, fluoro, chloro, hydroxyl, alkoxy, trifluoromethyl, and alkyl; and

"n" is an integer between 2 and 8.

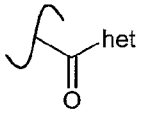
5. A process for inhibiting a fatty acid amide hydrolase comprising the following step:

contacting the fatty acid amide hydrolase with an inhibiting concentration of an inhibitor represented by the following formula:

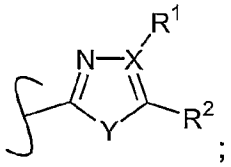
A-B-C

wherein **A** is an inhibition subunit, **B** is a linkage subunit, and **C** is a binding subunit and wherein:

the inhibition subunit **A** is an α-keto heterocyclic pharmacophore for inhibiting the fatty acid amide hydrolase, the α-keto heterocyclic pharmacophore being represented by the formula:



wherein "het" is represented by the following structure:



;

wherein:

X is selected from the group consisting of carbon and nitrogen;

Y is selected from the group consisting of oxygen and sulfur;

wherein R^1 and R^2 are radicals independently selected from the group consisting of hydrogen, C1-C6 alkyl, aromatic ring, and heteroaromatic ring;

with the following provisos:

R^1 and R^2 cannot both be hydrogen; and

if X is nitrogen, R^1 is absent;

the linkage subunit **B** is a chain for linking the inhibition subunit **A** and the binding subunit **C** and for enabling the binding subunit **C** to bind to the binding region on the fatty acid amide hydrolase which the inhibition subunit A simultaneously inhibits the fatty acid amide hydrolase, the chain having a linear skeleton of between 3 and 9 atoms selected from the group consisting of carbon, oxygen, sulfur, and nitrogen, the linear skeleton having a first end and a second end, the first end being covalently bonded to the α-keto group of **A**,

with the following proviso:

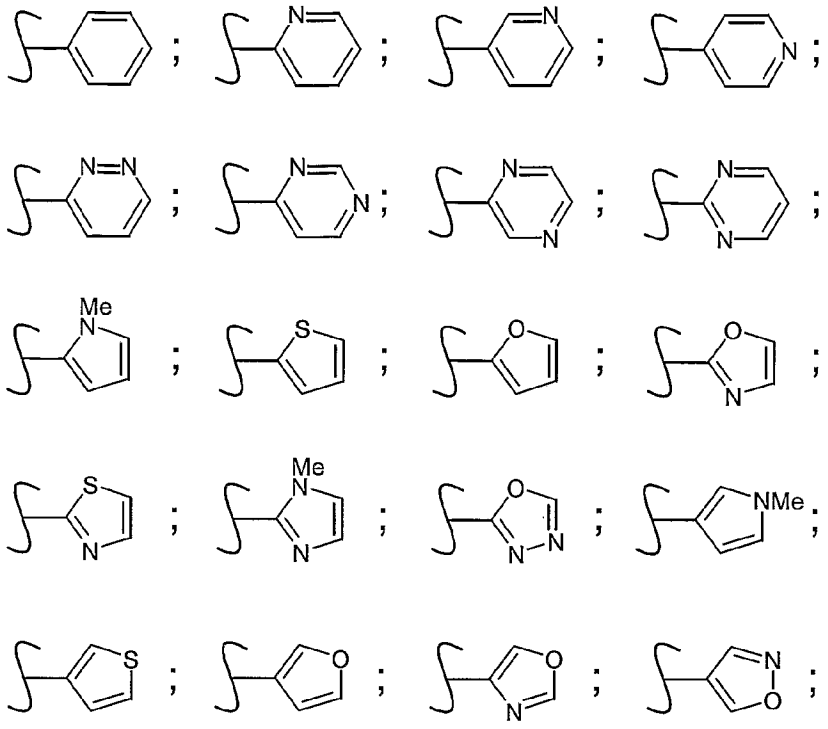
if the first end of said chain is an α-carbon with respect to the α-keto group of the inhibition subunit **A**, then the α-carbon is optionally mono- or bis-functionalized with substituents selected from the group consisting of fluoro, chloro, hydroxyl, alkoxy, trifluoromethyl, and alkyl; and

the binding subunit **C** is a π-bond containing radical having a π-unsaturation and being selected from a group consisting of aryl, alkenyl, alkynyl, and ring structures having at least one unsaturation, with or without one or more heteroatoms, the binding subunit **C** being covalently bonded to the second end of the linkage subunit **B**, the π-unsaturation within the π-bond containing radical being separated from the α-keto group of **A** by a sequence of no less than 3 and no more than 9 atoms bonded sequentially to one another, inclusive of the linear skeleton for enabling the π-unsaturation to bind to the binding region of the fatty acid amide hydrolase while the inhibition subunit **A** inhibits the fatty acid amide hydrolase;

with a proviso that **C** is optionally C1-C10 alkyl;

whereby, upon contacting the fatty acid amide, the binding subunit **C** binds to the binding region of the fatty acid amide hydrolase for enhancing the inhibition of the fatty acid amide hydrolase.

6. A process according to claim 5 wherein R^1 and R^2 are radicals independently selected from the group consisting of hydrogen, C1-C6 alkyl, and radicals represented by the following structures:



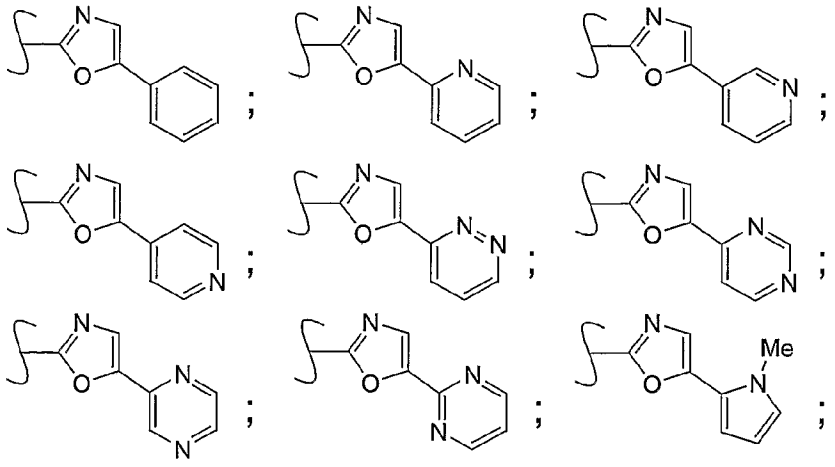
with the following provisos:

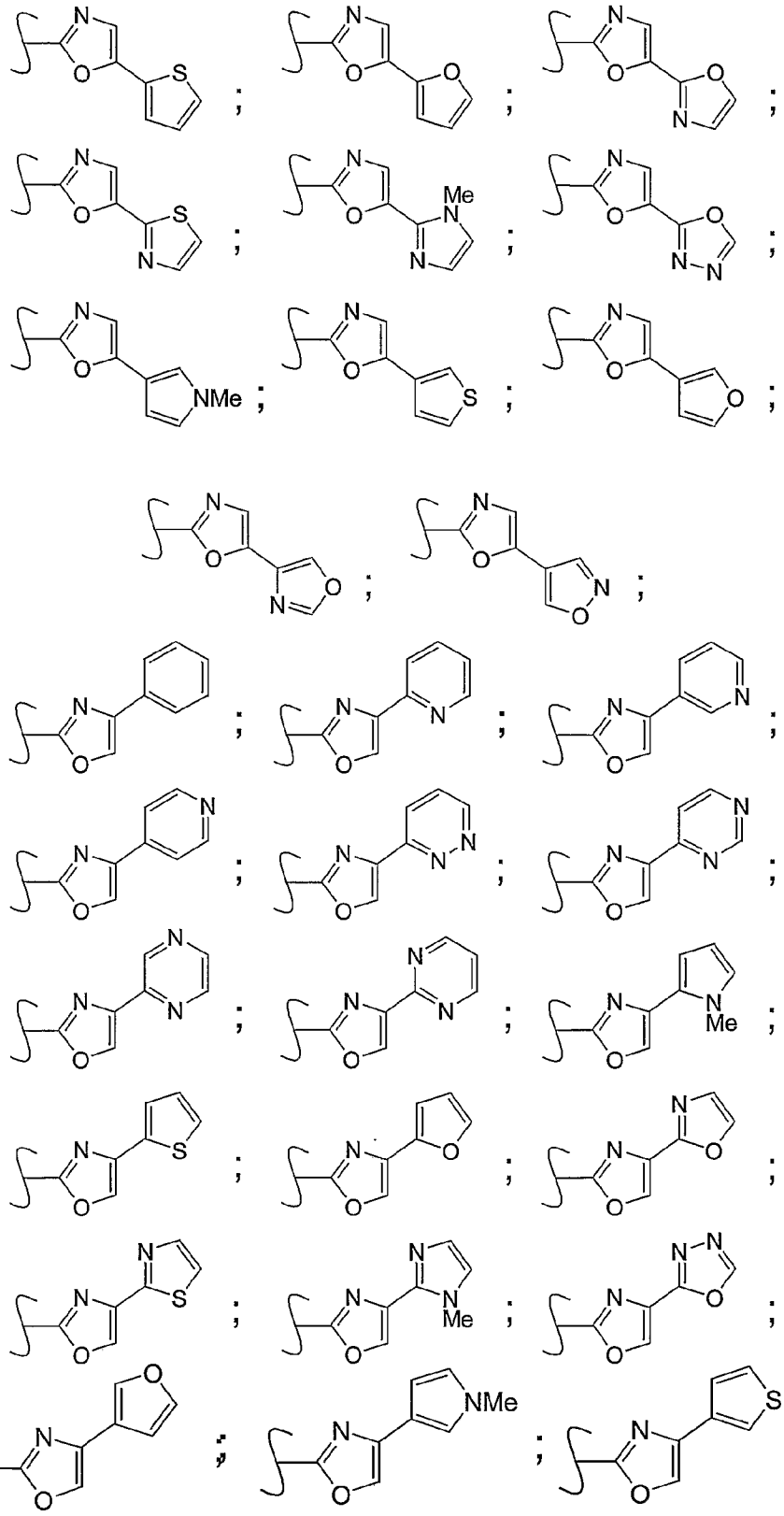
R^1 and R^2 cannot both be hydrogen; and

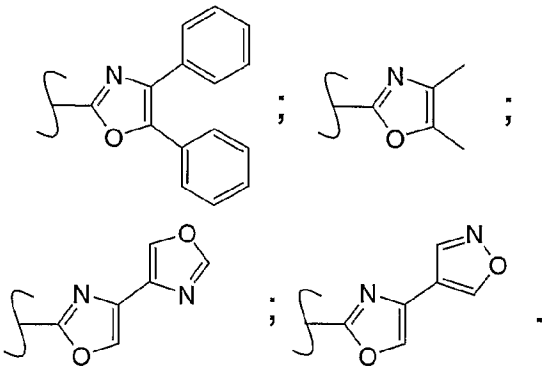
if X is nitrogen, R^1 is absent.

7. A process according to claim 6 wherein:

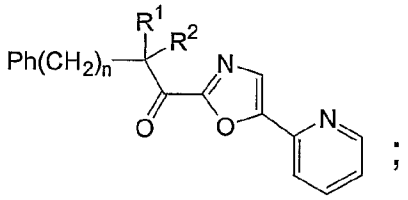
"het" of the α-keto heterocyclic pharmacophore is selected from the following group:







8. A process according to claim 7 wherein the inhibitor is represented by the following structure:

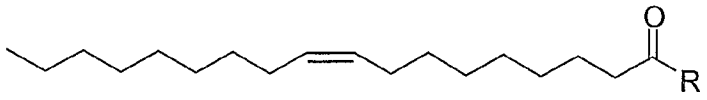


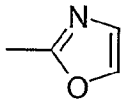
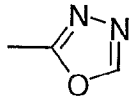
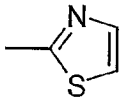
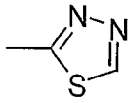
wherein

R^1 and R^2 are independently selected from the group consisting of hydrogen, fluoro, chloro, hydroxyl, alkoxy, trifluoromethyl, and alkyl; and

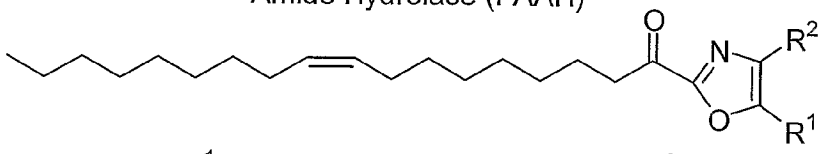
"n" is an integer between 2 and 8.

α-Keto Oxazole, Thiazole, Oxadiazole, and Thiadiazole Inhibitors of Fatty Acid Amide Hydrolase (FAAH)



compound	R	K_i, μM	compound	R	K_i, μM
70		0.10 ±0.06	**140**		0.09 ±0.2
68		> 100	**141**		0.17 ±0.03

Substituted α-Keto Oxazole Inhibitors of Fatty Acid Amide Hydrolase (FAAH)



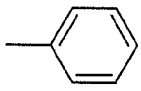
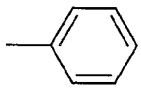
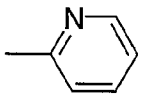
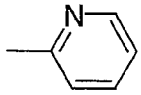
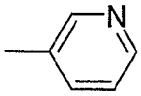
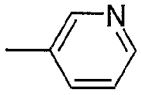
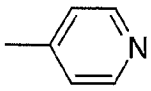
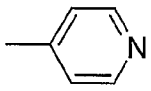
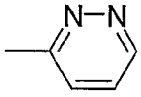
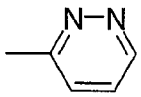
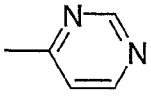
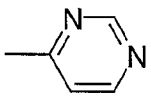
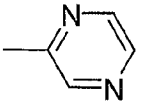
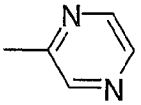
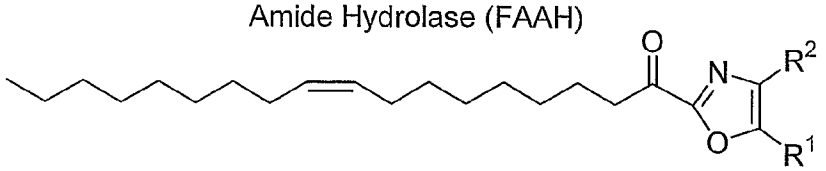
compound	R^1	K_i, μM	compound	R^2	K_i, μM
142		0.32 ±0.05	**162**		0.49 ±0.03
143		0.018 ±0.005	**163**		0.031 ±0.006
144		0.061 ±0.004	**164**		0.041 ±0.010
145		0.056 ±0.003	**165**		0.078 ±0.014
146			**166**		
147			**167**		
148			**168**		

Figure 1

Substituted α-Keto Oxazole Inhibitors of Fatty Acid Amide Hydrolase (FAAH)



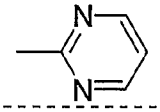
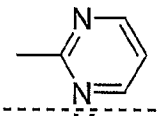
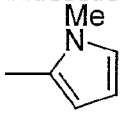
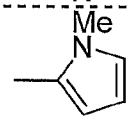
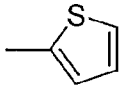
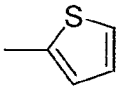
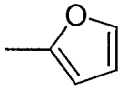
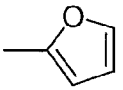
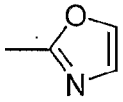
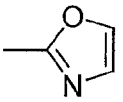
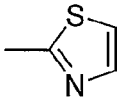
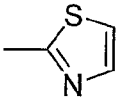
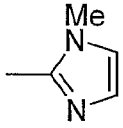
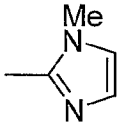
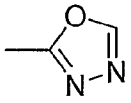
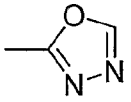
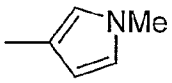
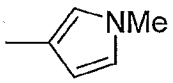
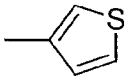
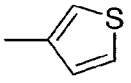
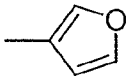
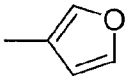
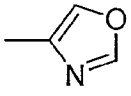
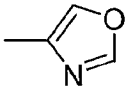
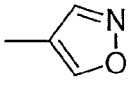
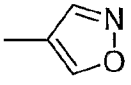
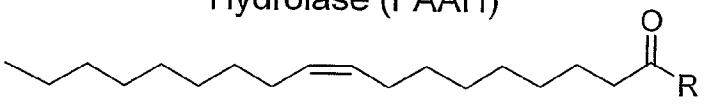
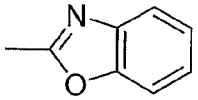
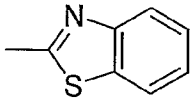
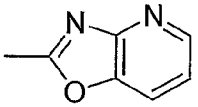
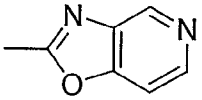
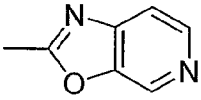
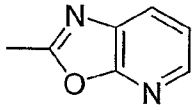
compound	R^1	K_i, μM	compound	R^2	K_i, μM
149			**169**		
150		8.6 ±2.1	**170**		
151		0.89 ±0.03	**171**		
152		0.054 ±0.004	**172**		
153			**173**		
154		0.016 ±0.002	**174**		
155		0.047 ±0.006	**175**		
156			**176**		
157			**177**		
158		13.2 ±4.1	**178**		
159		0.61 ±0.09	**179**		
160			**180**		
161			**181**		

Figure 2

α-Keto Oxazolopyridine Inhibitors of Fatty Acid Amide Hydrolase (FAAH)

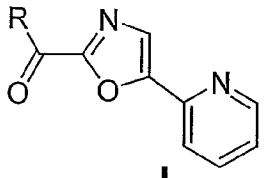


compd	R	K_i, μM	compd	R	K_i, μM
83		0.37 ±0.13	**84**		> 100
89		0.0023 ±0.0001	**90**		0.0072 ±0.0016
91		0.0037 ±0.0010	**92**		0.011 ±0.004

- Potency increases with introduction of basic nitrogen
- Potency increases ca. 200x and N4 > N6 > N5 > N7
- Relatively insensitive to location of additional nitrogen

Figure 3

Modifications in the Fatty Acid Side Chain



compd	R	K_i, μM	compd	R	K_i, μM
182	$CH_3(CH_2)_{16}$	0.059 ±0.014	**195**	$Ph(CH_2)$	17.4 ±4.6
183	$CH_3(CH_2)_{14}$	0.021 ±0.005	**196**	$Ph(CH_2)_2$	0.20 ±0.6
184	$CH_3(CH_2)_{12}$	0.013 ±0.005	**197**	$Ph(CH_2)_3$	0.12 ±0.02
185	$CH_3(CH_2)_{10}$	0.0022 ±0.0005	**198**	$Ph(CH_2)_4$	0.033 ±0.002
186	$CH_3(CH_2)_9$	0.0033 ±0.0006	**199**	$Ph(CH_2)_5$	0.011 ±0.003
187	$CH_3(CH_2)_8$	0.0090 ±0.026	**200**	$Ph(CH_2)_6$	0.0047 ±0.0013
188	$CH_3(CH_2)_7$	0.041 ±0.004	**201**	$Ph(CH_2)_7$	0.0075 ±0.0034
189	$CH_3(CH_2)_6$	0.049 ±0.005	**202**	$Ph(CH_2)_8$	0.0078 ±0.0021
190	$CH_3(CH_2)_5$	0.17 ±0.07		$Ph(CH_2)_9$	
191	$CH_3(CH_2)_4$	0.94 ±0.3		$Ph(CH_2)_{10}$	
192	$CH_3(CH_2)_3$	3.0 ±0.9			
193	$CH_3(CH_2)_2$	11.4 ±2.2			
194	CH_3CH_2	47.6 ±10.4			

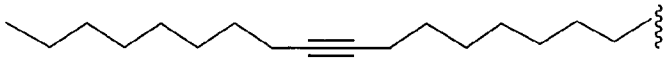
203	$CH_2=CH(CH_2)_7$	0.011 ±0.001	**204**	$HC\equiv C(CH_2)_7$	0.023 ±0.011
205					0.010 ±0.001

Figure 4

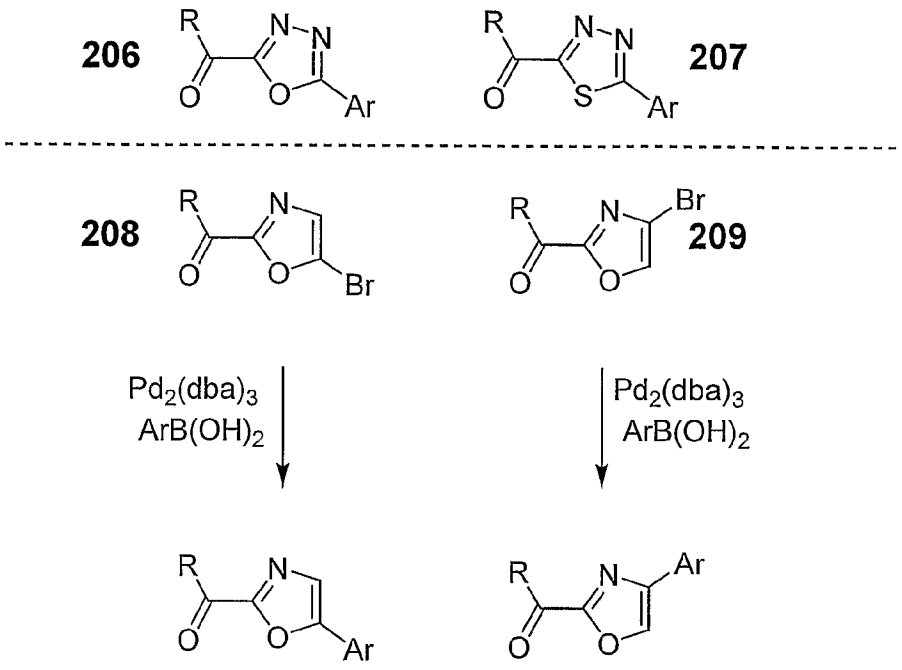
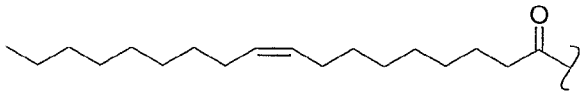
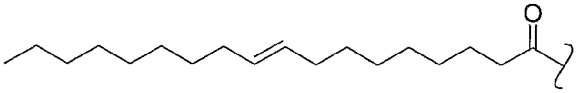
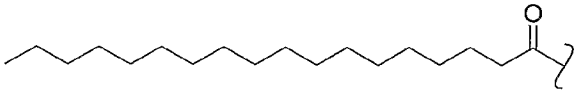
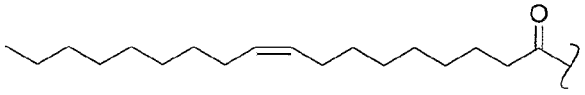
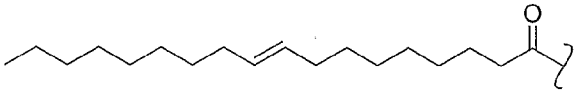
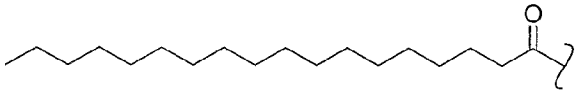


Figure 5

compound	R	K_i, μM
89		0.0023 ±0.0001
93		0.0032 ±0.0006
94		0.011 ±0.006

compound	R	K_i, μM
77		0.13 ±0.02
95		0.15 ±0.02
96		0.70 ±0.03

• C18 $\Delta^{9,10}$; Z(cis) > E(trans) > saturated

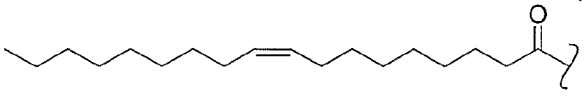
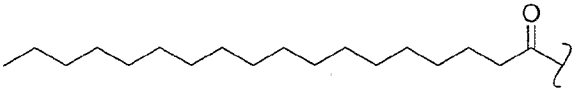
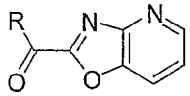
compound	R	K_i, μM
83		0.37 ±0.13
97		2.4 ±0.5

Figure 6



compound	R	K_i, μM	compound	R	K_i, μM
34	$CH_3(CH_2)_{16}$	0.011 ±0.006	**51**	$Ph(CH_2)_3$	0.0069 ±0.001
42	$CH_3(CH_2)_{14}$	0.0019 ±0.0002	**52**	$Ph(CH_2)_4$	0.00030 ±0.00009
43	$CH_3(CH_2)_{12}$	0.0017 ±0.0008	**53**	$Ph(CH_2)_5$	0.00020 ±0.0008
44	$CH_3(CH_2)_{10}$	0.00057 ±0.00024	**54**	$Ph(CH_2)_6$	0.00028 ±0.00020
45	$CH_3(CH_2)_8$	0.00075 ±0.00017	**55**	$Ph(CH_2)_7$	0.00039 ±0.00006
46	$CH_3(CH_2)_6$	0.00069 ±0.00015	**56**	$Ph(CH_2)_8$	0.00052 ±0.00018
47	$CH_3(CH_2)_5$	0.0021 ±0.0003			
48	$CH_3(CH_2)_4$	0.015 ±0.002			
49	$CH_3(CH_2)_3$	0.050 ±0.009			
50	CH_3	>100			

- C18 < C16 < C14 < C12-C8 > C7 > C6 > C5 > C2

K_i = 200 pM

- $Ph(CH_2)_3$ < $Ph(CH_2)_4$ < $Ph(CH_2)_5$ > $Ph(CH_2)_6$ > $Ph(CH_2)_7$ > $Ph(CH_2)_8$ > C1-C18

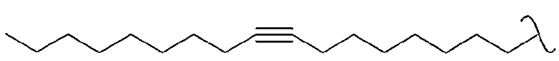
117	$CH_2=CH(CH_2)_7$	0.00015 ±0.00001	**118**	$HC\equiv C(CH_2)_7$	0.00018 ±0.00002
119					0.00014 ±0.00002

Figure 7

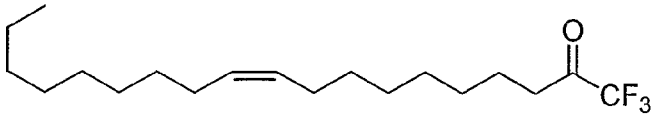
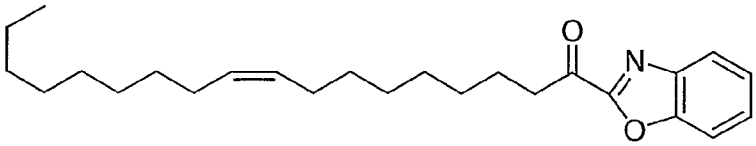
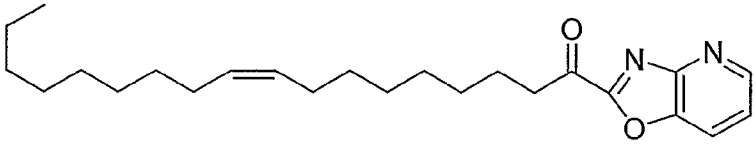
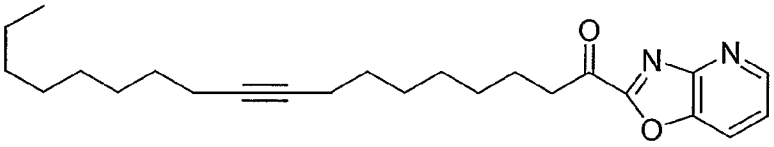
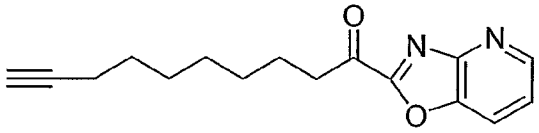
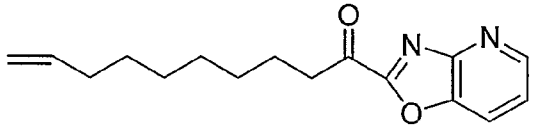
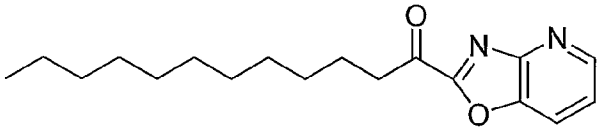
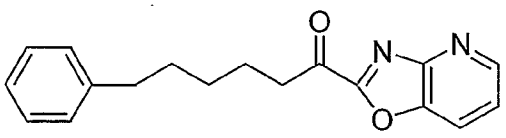
First Generation Inhibitors	IC_{50} FAAH
	**41** 5 μM
	**83** 10 μM
	**89** 0.044 μM
	**119** 0.007 μM
	**118** 0.0025 μM
	**117** 0.0035 μM
	**104** 0.0029 μM
	**53** 0.001 μM

Figure 8

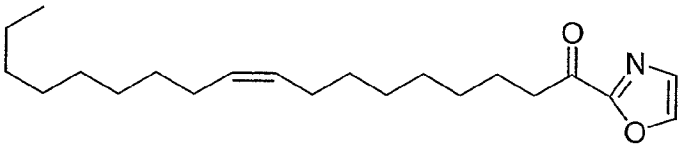
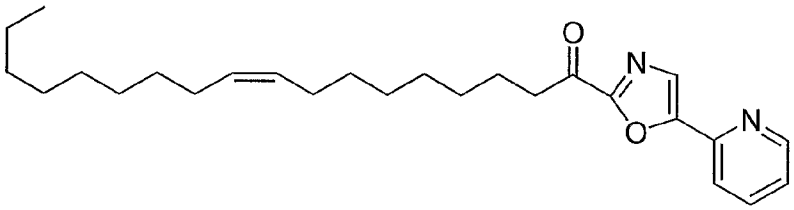
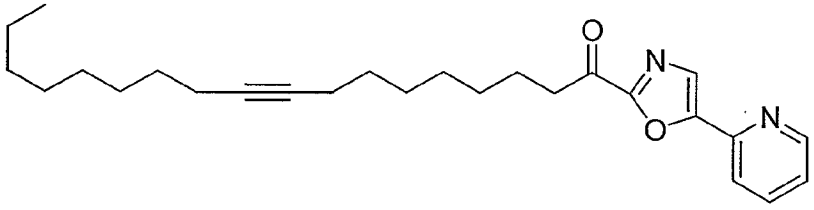
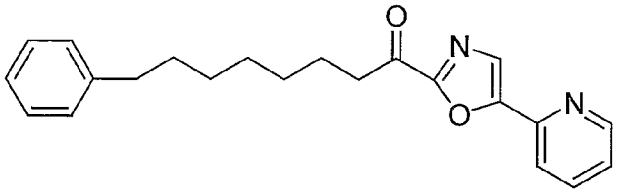
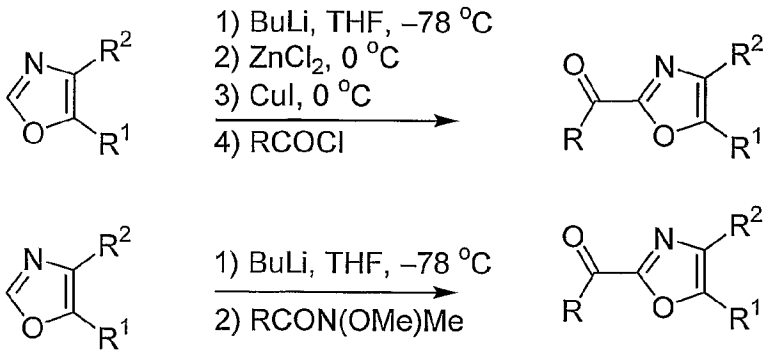
Second Generation Inhibitors	IC_{50} FAAH
	**70** 2.3 μM
	**143** 0.15 μM
	**205** 0.05 μM
	**201** 0.01 μM

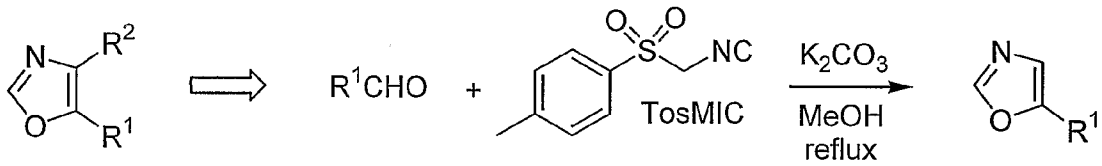
Figure 9

Harn, N. K.; Gramer, C. J.; Anderson, B. A. *Tetrahedron Lett.* **1995**, *36*, 9453.

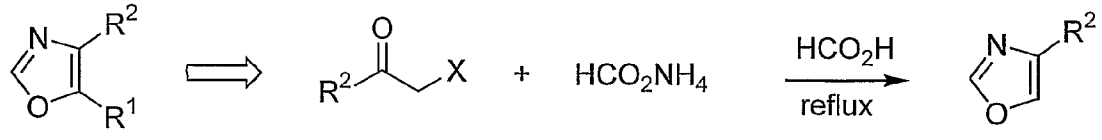


Boger, D. L. et al. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 5049.

Van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, 2369.
Saikachi, H.; Kitagawa, T.; Sasaki, H.; Van Leusen, A. M.
Chem. Pharm. Bull. **1979**, *27*, 793.



R^2 = H
R^1 = Ar



R^2 = Ar
R^1 = H

Giardina, G. A.; Sarau, H. M.; Farina, C.; Medhurst, A. D.; Grugni, M.; Raveglia, L. F.; Schmidt, D. B.; Rigolio, R.; Luttmann, M.; Vecchieti, V.; Hay, D. W. P. *J. Med. Chem.* **1997**, *40,* 1794.

Figure 10

Tail Withdrawal Test

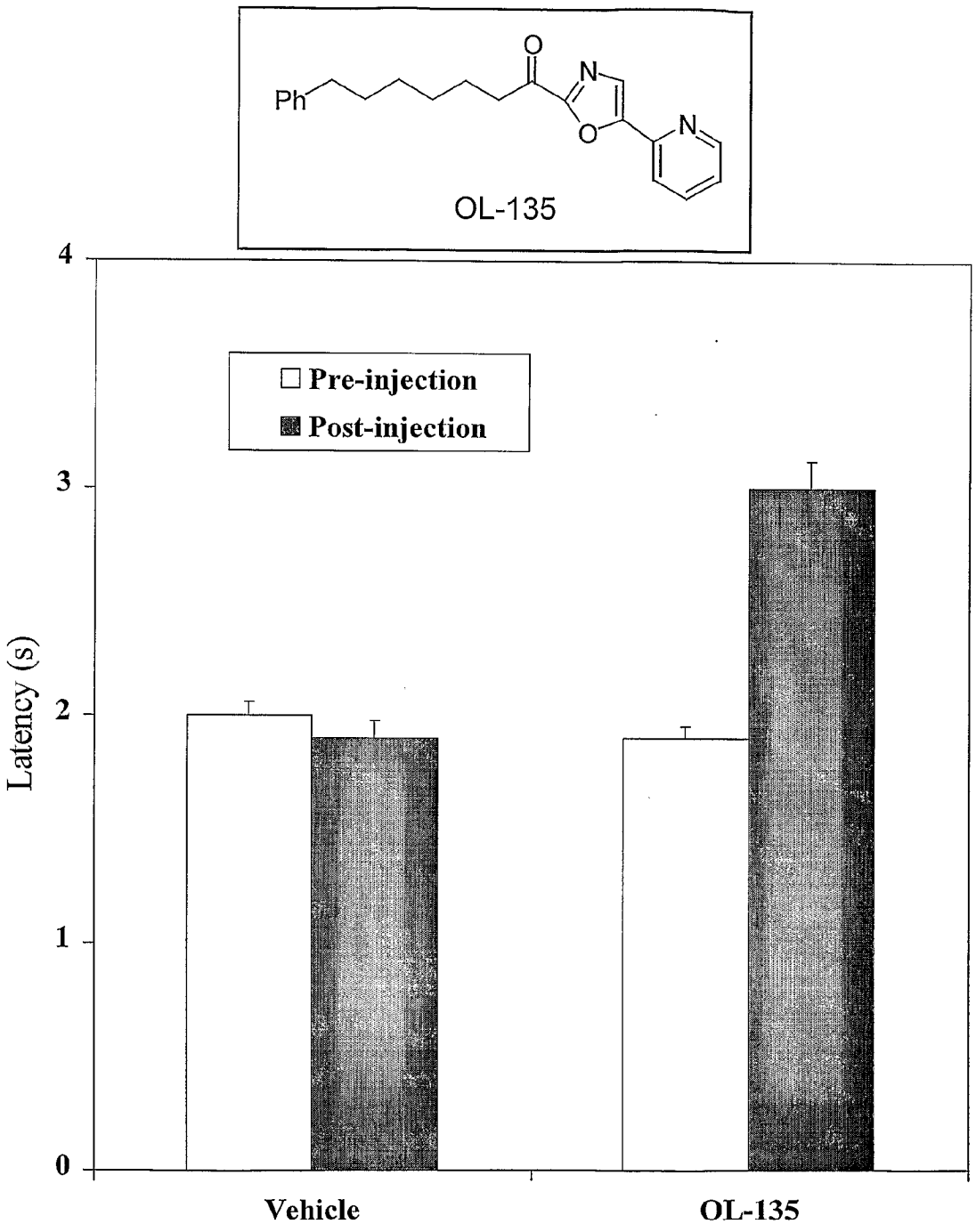


Figure 11

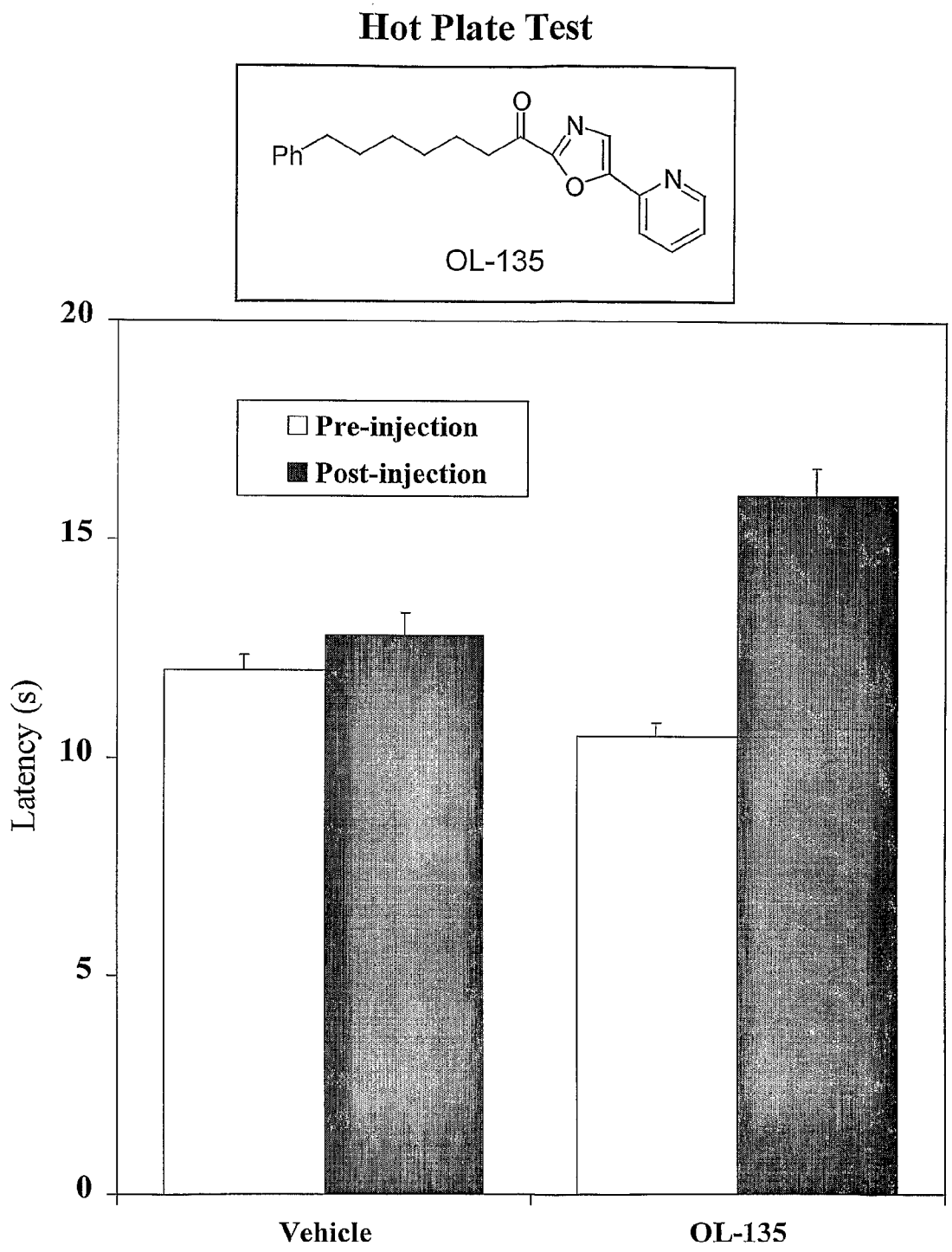

Hot Plate Test
Ph
O
N
O
N
OL-135
20
15
10
5
0
Latency (s)
Pre-injection
Post-injection
Vehicle
OL-135

Figure 12

Tail Withdrawal Test

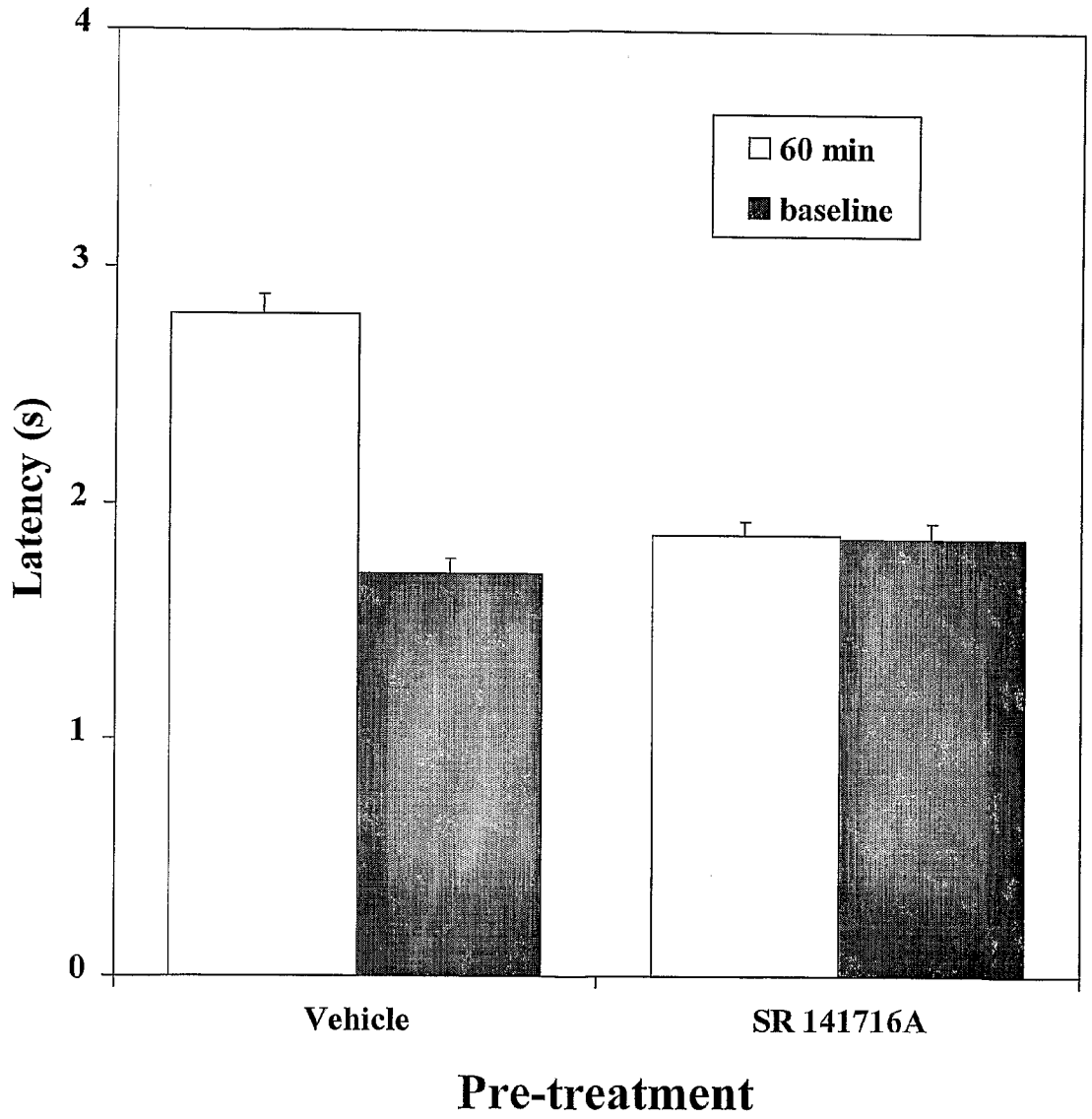


Figure 13

Hot Plate Test

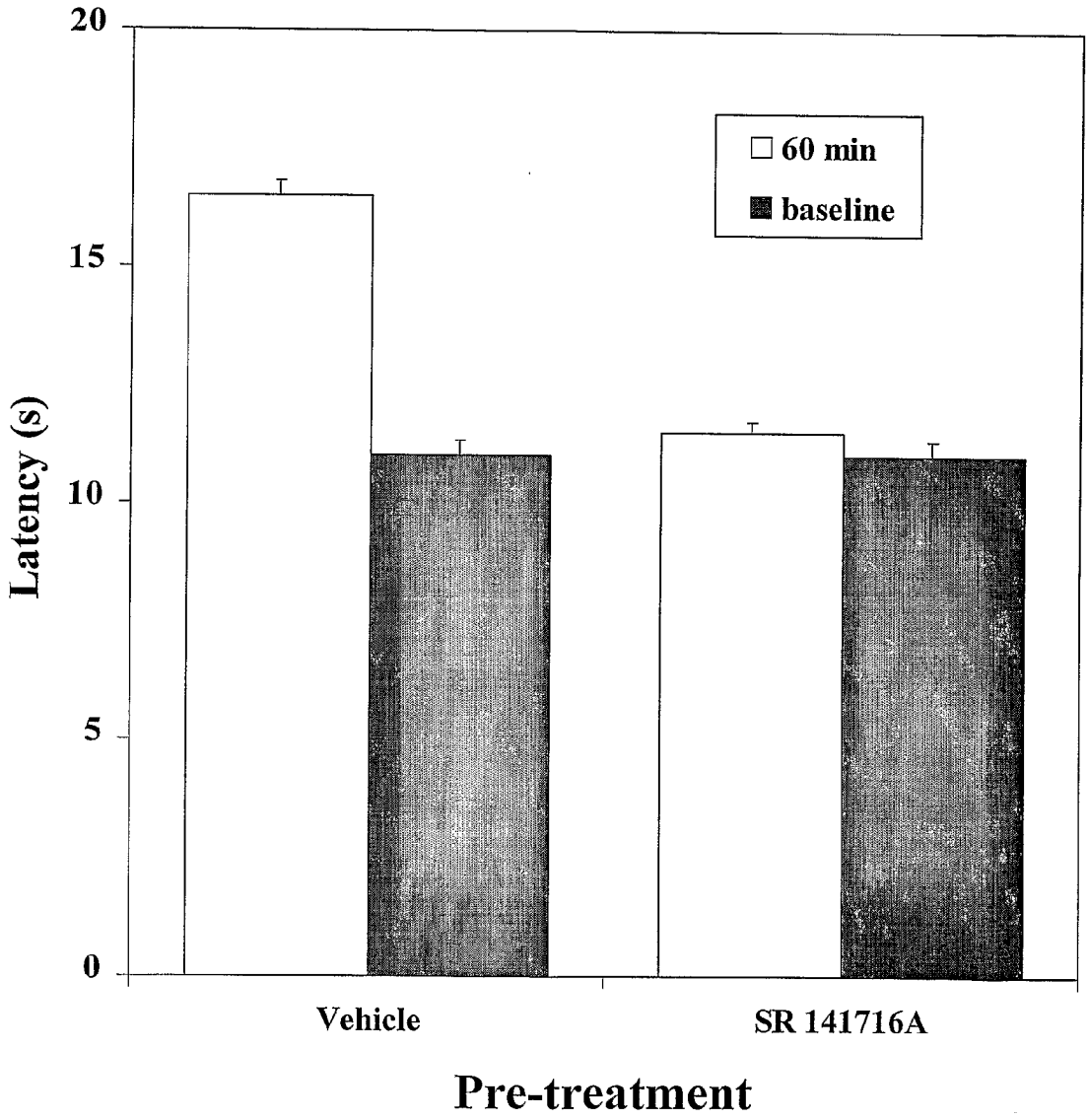
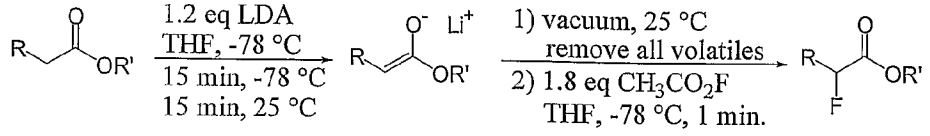


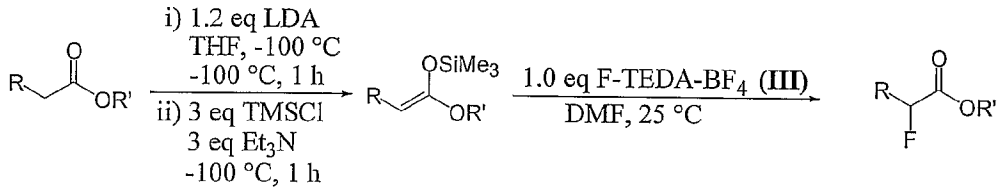
Figure 14

Alpha-functionalization of the carbonyl-containing tail

Fluorine

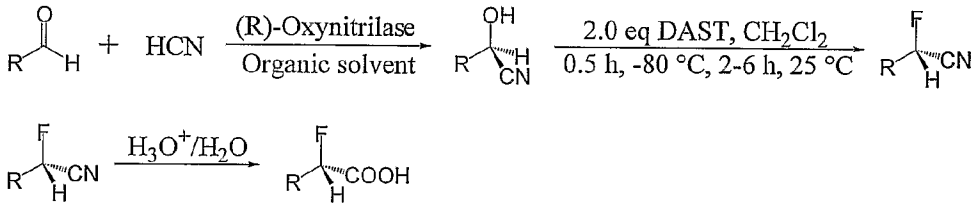


Rozen, S.; Brand, M. *Synthesis* **1985**, 665-667.



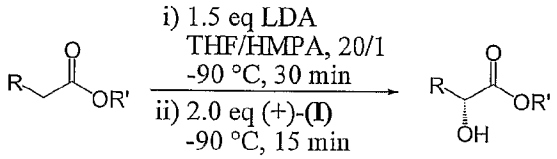
Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791-2796.

α-Chiral Fluorine



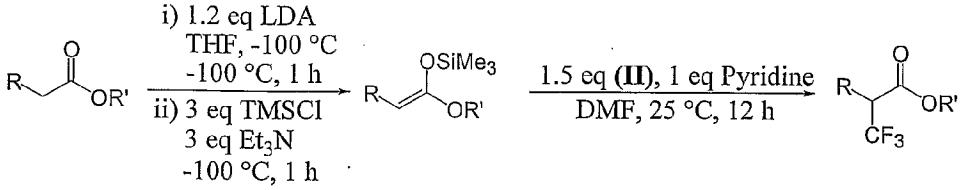
Stelzer, U.; Effenberger, F. *Tetrahedron: Asymmetry* **1993**, *4*, 161-164.

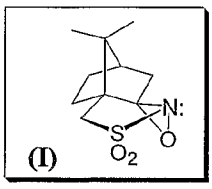
Hydroxyl

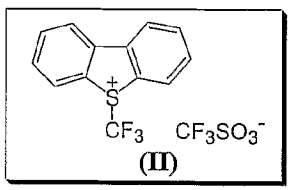


Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402-2404.

Trifluoromethyl







Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156-2164.

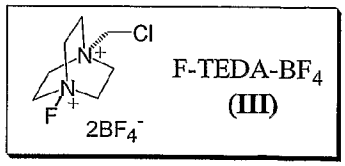
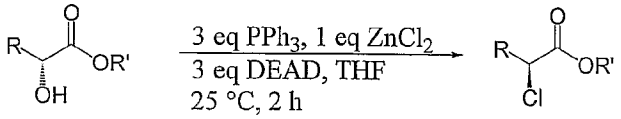


Figure 15

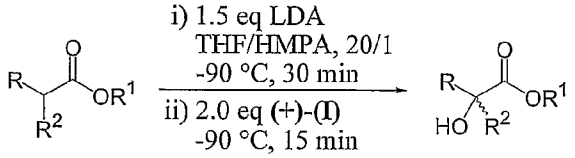
Alpha-functionalization of the carbonyl-containing tail

Chlorine



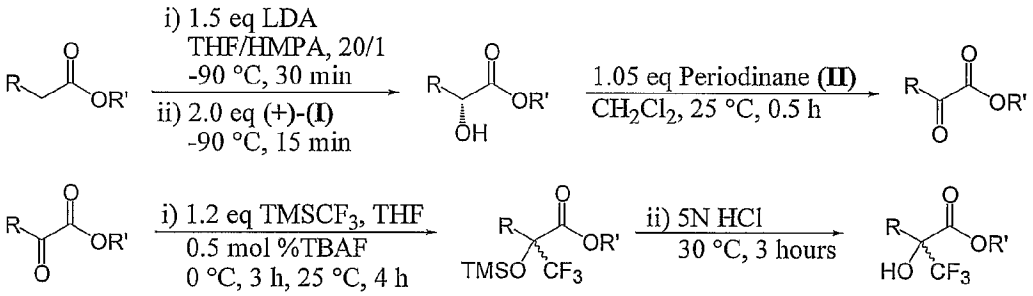
Ho, P.-T.; Davies, N. *J. Org. Chem.* **1984**, *49*, 3027-2029.

α-Alkyl-α-hydroxy



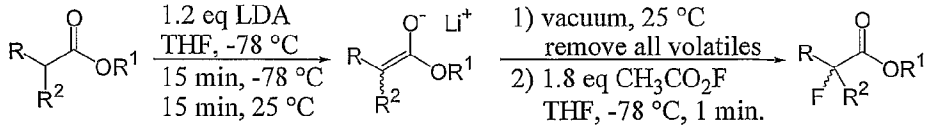
Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402-2404.

α-Hydroxy-α-trifluoromethyl-



Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402-2404.
Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *83*, 4155-4156.
Ramaiah, P.; Prakash, G. K. S. *Synlett* **1991**, 643-644.

α-Alkyl-α-fluoro



Rozen, S.; Brand, M. *Synthesis* **1985**, 665-667.

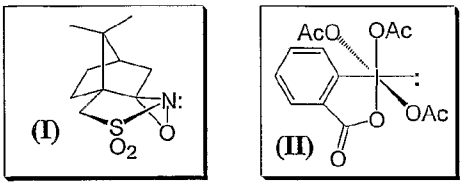


Figure 16